Interim Session — Philadelphia
December 2, 1957

VOLUME XXXII NUMBER 3

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

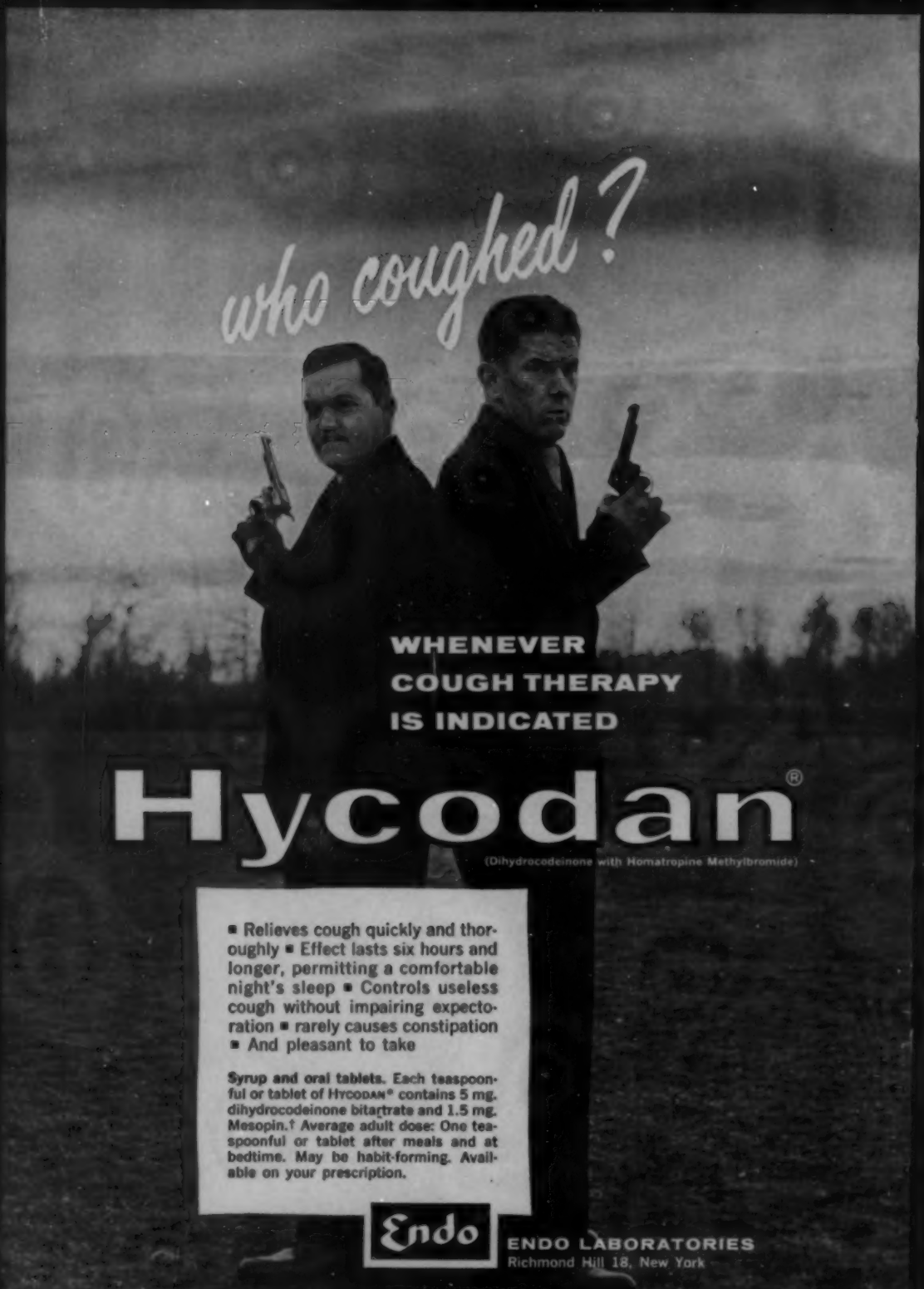
PUBLISHED MONTHLY

SEPTEMBER
1957

PUBLICATION OFFICE, CHICAGO, ILLINOIS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

Entered as Second Class Matter at the Postoffice at Chicago, Illinois

Fifth International Congress on Diseases of the Chest
Tokyo, Japan — September 7-11, 1958



WHENEVER
COUGH THERAPY
IS INDICATED

Hycodan®

(Dihydrocodeinone with Homatropine Methylbromide)

■ Relieves cough quickly and thoroughly ■ Effect lasts six hours and longer, permitting a comfortable night's sleep ■ Controls useless cough without impairing expectoration ■ rarely causes constipation ■ And pleasant to take

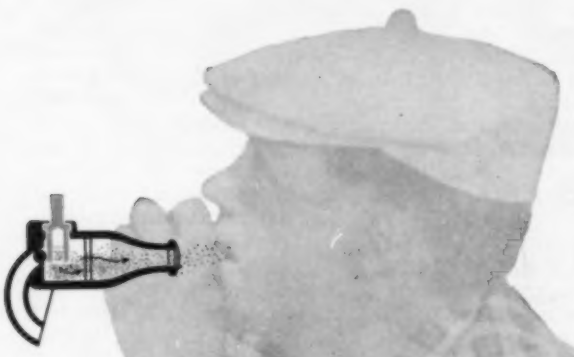
Syrup and oral tablets. Each teaspoonful or tablet of HYCODAN* contains 5 mg. dihydrocodeinone bitartrate and 1.5 mg. Mesopin.† Average adult dose: One teaspoonful or tablet after meals and at bedtime. May be habit-forming. Available on your prescription.

Endo

ENDO LABORATORIES
Richmond Hill 18, New York

*U. S. PAT. 2,630,400 † BRAND OF HOMATROPINE METHYLBROMIDE

What happens when asthma attacks a golf pro?



Simply this. He aborts bronchospasm—almost before it begins—with one or two inhalations of NORISODRINE through the AEROHALOR.

It's that fast, Doctor. And NORISODRINE is effective in all types of asthma. Ninety per cent of the particles inhaled are less than 10 microns in size. These particles move quickly into the tracheobronchial tree where they act to provide relief where it is needed most.

Side effects, as well as "fastness," are rare as long as dosage is properly regulated.

Why not take a close look at this therapy, Doctor? Examine the easy-to-use, unbreakable AEROHALOR and, perhaps, keep one or two of the NORISODRINE-AEROHALOR combinations in your office.

Abbott

NORISODRINE® Sulfate Powder in the AEROHALOR®

(Isoproterenol Sulfate, Abbott) (Abbott's powder inhaler)

DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

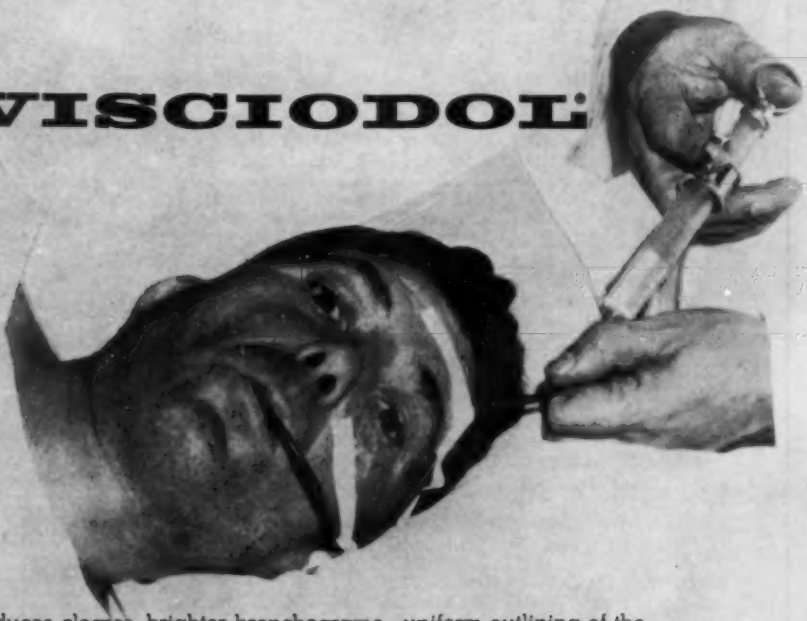
EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

now

a rapidly eliminated bronchographic medium...

less irritating—rarely penetrates the alveoli

VISCIODOL



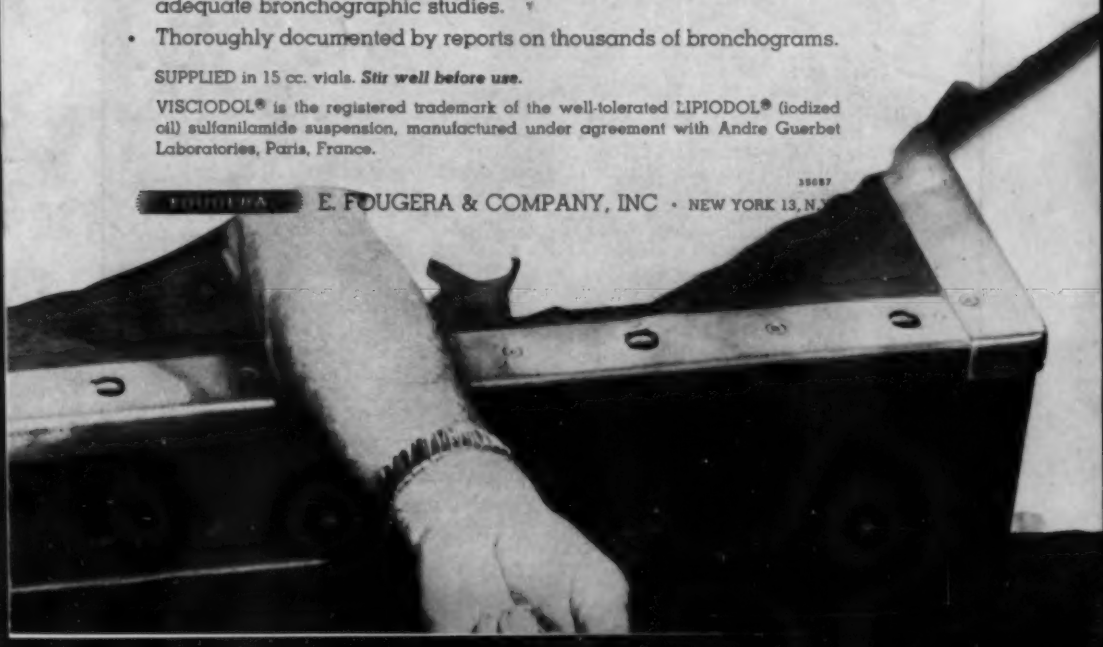
- Produces clearer, brighter bronchograms—uniform outlining of the bronchial tree.
- Usually requires less anesthesia.
- Rapidly and completely eliminated—but retained long enough for adequate bronchographic studies.
- Thoroughly documented by reports on thousands of bronchograms.

SUPPLIED in 15 cc. vials. ***Stir well before use.***

VISCIODOL® is the registered trademark of the well-tolerated LIPIODOL® (iodized oil) sulfanilamide suspension, manufactured under agreement with Andre Guerbet Laboratories, Paris, France.

35087

E. FOUGERA & COMPANY, INC • NEW YORK 13, N.Y.



VOLUME XXXII SEPTEMBER, 1957 NUMBER 3

CONTENTS

Entered as Second Class Matter at the Postoffice at Chicago, Illinois

Annual Subscription: $15.00, postpaid to any part of the world.

one of the many overwhelmingly
documented benefits in asthma[1-4]

METICORTEN®

(prednisone)

relieve more asthmatics with fewer injections...

The greater relief—more complete and more prolonged—achieved for your asthmatics with METICORTEN lessens the requirements for epinephrine and aminophylline injections and accessory medications.

Since METICORTEN does not produce electrolyte disturbances at average therapeutic dosages, it usually obviates dietary restrictions and also may be given more safely to asthmatic patients with cardiorenal insufficiency.

(1) Feinberg, A. R., and Feinberg, S. M.: J.A.M.A. *160*:264, 1956. (2) Schwartz, E.: J. Allergy *26*:206, 1955. (3) Skaggs, J. T.; Bernstein, J., and Cooke, R. A.: J. Allergy *26*:201, 1955. (4) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Dis. Chest *27*:515, 1955.

METICORTEN, 1, 2.5, and 5 mg. white tablets.

MC-J-487

Schering

SPECIFICALLY INDICATED

- for short-term protection of selected surgical patients to prevent or minimize the spread of infection or other complications
- for seriously ill hospitalized patients with tuberculosis unresponsive to other chemotherapeutic agents

A new and potent tuberculostatic agent

PYRAZINAMIDE

PYRAZINOIC ACID AMIDE

Pyrazinamide will produce good immediate, even if only briefly enduring, results, such as:

1. reduction of fever, cough and quantity of sputum with concomitant gains in appetite, weight and well-being.

2. x-ray evidence of partial clearing of far-advanced chronic fibrotic lesions in a small percentage of patients and also in a larger percentage of patients with acute infiltrative disease.

3. remarkable improvement or healing in patients with extra-pulmonary lesions such as draining sinuses, mucosal lesions and lymphadenopathy.

4. conversion of sputum in 10% of cases.

PYRAZINAMIDE is available through hospital pharmacies.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

SUMMARY

Potassium para-aminosalicylate (KPAS) was administered to 120 patients with tuberculosis.

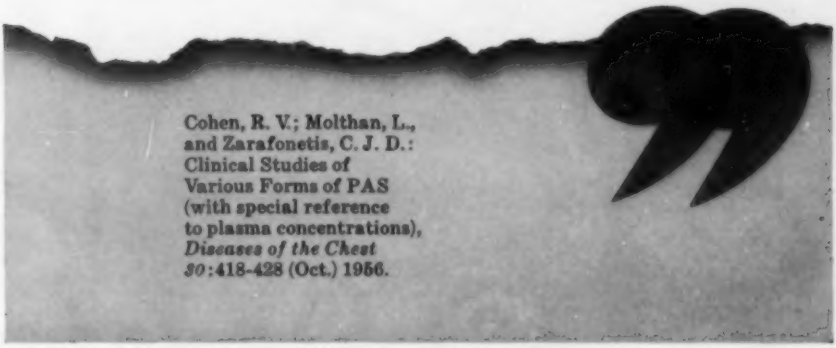
One hundred fifteen (96 per cent) tolerated 12 gm. daily doses of KPAS without difficulty. There were no evidences of potassium toxicity.

Plasma PAS concentration studies revealed that KPAS is more rapidly absorbed and yields significantly higher values than either PAS or NaPAS.

KPAS is ideally suited for use in patients with congestive heart failure, pregnancy, or other situations in which use of the sodium salt is precluded.

The 10 per cent solution of KPAS was used for "desensitizations" of those who had acquired sensitivity reactions to PAS compounds.

It is concluded that KPAS is superior to other forms of PAS.



Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

In tuberculosis chemotherapy simple addition multiplies effectiveness

The combination of a primary agent that exerts the major tuberculostatic action

STREPTOMY... *(Brand of streptomycylidene isonicotinyl hydrazine sulfate)* Supplied in single-dose vials containing 1.4 Gm. Streptohydrazid (1 Gm. streptomycin combined with 236 mg. of isoniazid).

...TRAZID *(Brand of isoniazid)* 50 mg. scored tablets in bottles of 100 and 1000.

...BISTREPTO... *(Brand of streptodimocin)* Dry powder in vials containing 1 Gm. and 5 Gm.

STREPTOMYCIN ... DRY POWDER Rubber-capped vials of 1 Gm. and 5 Gm.

STREPTOMYCIN SULFATE SOLUTION Vials of 1 Gm. (2.5 cc.) and 5 Gm. (12.5 cc.). Also available in the new Steraject® cartridge (1 Gm.).

DIHYDROSTREPTOMYCIN SULFATE DRY POWDER Rubber-capped vials of 1 Gm. and 5 Gm.

DIHYDROSTREPTOMYCIN SULFATE SOLUTION Vials of 1 Gm. (2.5 cc.) and 5 Gm. (12.5 cc.). Also in the new Steraject cartridge (1 Gm.).

with another agent that subserves the secondary function of preventing the emergence of resistant organisms

...MYCIN *(Brand of viomycin sulfate)* Single-dose vials containing 1 Gm. and five-dose vials containing 5 Gm. of viomycin base.

TERRAMYCIN *(Brand of oxytetracycline)* Capsules containing 250 mg., bottles of 16 and 100. Capsules containing 100 mg. and 50 mg.; bottles of 25 and 100.

adds to antituberculosis activity, subtracts from toxicity, reduces or prevents emergence of resistant organisms—particularly important in long-term therapy.

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y. *Pfizer*

The CHASE
CATHETERIZING BRONCHOSCOPE

An Instrument for Catheterizing Upper Lobe Bronchi and for other Bronchoscopic Procedures

The instrument consists of an 8 mm tube, an oxygen inlet tube and a suction tube. A light carrier permits the use of the instrument as a standard bronchoscope.

The light carrier channel is used to convey the catheter and a permanent deflecting mechanism in the distal end deflects the catheter in a right angle direction.

A right angle telescope, used with a removable adapter, is necessary for visualization of the bronchus to be catheterized.

The Broyles Right Angle Telescope, Cat. No. 4703, can be used with the Chase Catheterizing Bronchoscope, but is not supplied as a part of the instrument.

Cat. No. 4690

The Chase Catheterizing Bronchoscope can be used for

- **Regular bronchoscopy.**
- **Catheterization of an inflamed bronchus and do a bronchial lavage for sputum near the lesion.**
- **Location of strictures from swelling of bronchi and reduction of swelling by application of neosynephrine to reduce or collapse the swollen cavity.**
- **Sectional bronchography.**
- **Drainage of some lung abscesses.**

ESTABLISHED IN 1910 BY REINHOLD WAPPLER

FREDERICK J. WALLACE, President

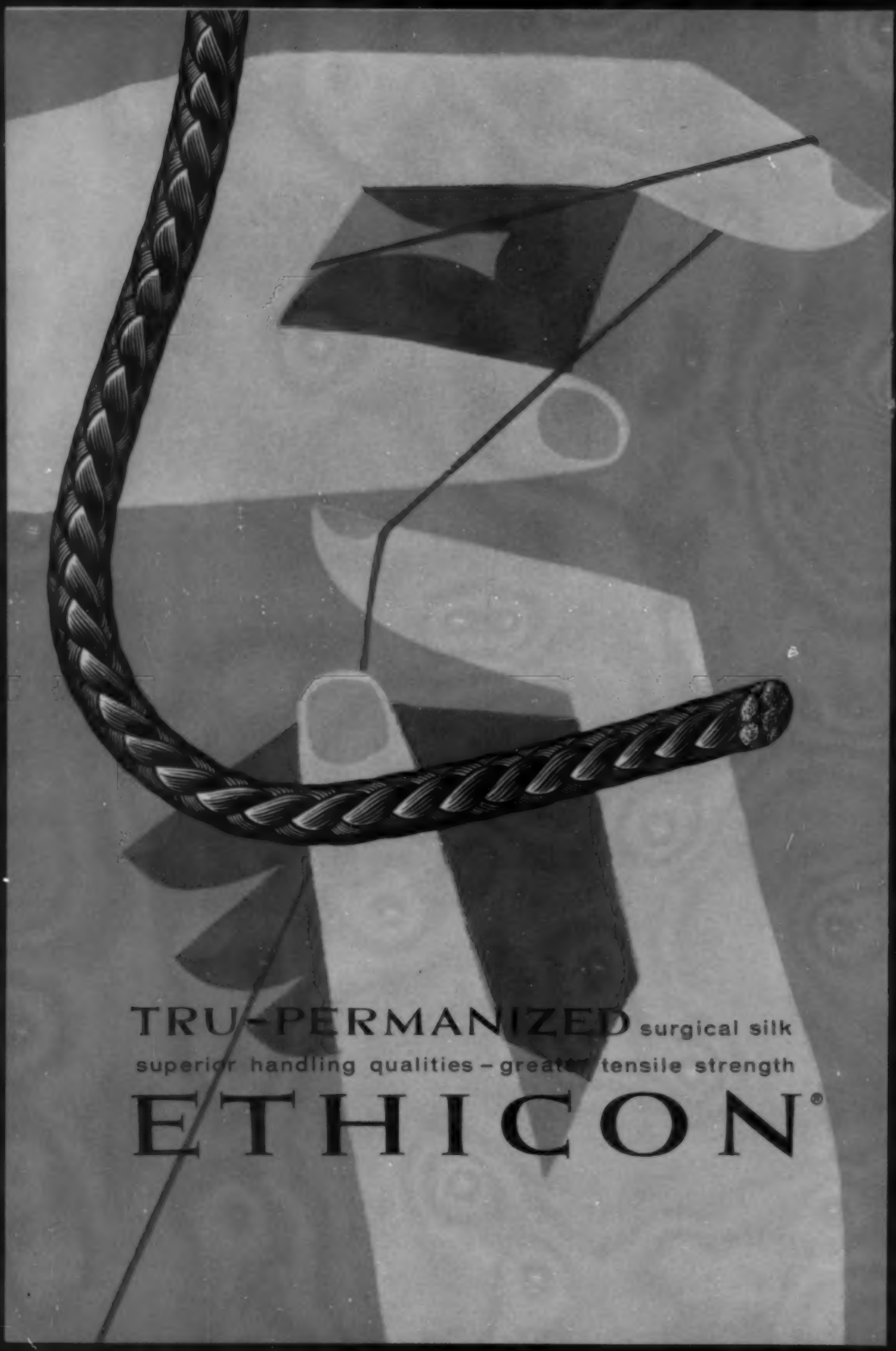
American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE NEW YORK 59, N. Y.

setting new standards

ETHICON®

sutures


TRU-PERMANIZED surgical silk
superior handling qualities – greater tensile strength
ETHICON®

3 essential drugs for chemotherapy of tuberculosis

NYDRAZID

Squibb Isoniazid

The most potent anti-tuberculosis agent available—developed in Squibb laboratories.

Tablets, 50 and 100 mg. (scored), bottles of 100 and 1000
Syrup, 10 mg. per ml., pint bottles
Injection, 100 mg. per ml., 10 ml. vials

DISTRYCIN

Squibb Streptoduocin

As active as streptomycin or dihydrostreptomycin, but with markedly less toxicity.

Powder, vials containing 1 Gm. and 5 Gm.
Solution, 0.5 Gm. per ml., vials of 2 ml. and 10 ml.
0.5 Gm. per 1.25 ml., vials of 2.5 ml. and 12.5 ml.

REZIPAS

Squibb PAS Resin

Many patients unable to tolerate PAS can take Rezipas.

1 pound jars

SQUIBB

A PIONEER IN ANTI-TUBERCULOSIS RESEARCH

DISEASES of the CHEST

VOLUME XXXII SEPTEMBER, 1957 NUMBER 3

Cardiac Surgery for Acquired Valvular Disease: Modifications Experienced with 2,000 Cases

HOUCK BOLTON, M.D., F.C.C.P.*
Philadelphia, Pennsylvania

and BENJAMIN G. MUSSER, M.D.**
Harrisburg, Pennsylvania

Introduction

The surgical treatment of acquired valvular abnormalities resulting from acquired heart disease is of recent origin. The purpose of this paper is to report modifications in cardiovascular techniques made to improve our clinical results. Efforts were first directed toward the correction of the obstructive type of mitral valvular pathology. Eight years have now passed since the performance of the first successful operation for mitral stenosis.[1] The development of such an efficient surgical procedure has, like most other significant advances, been preceded by a long period of investigation, formulation and clarification of concepts. The first good description of the pathological entity which we know as mitral stenosis was given by de Vieussens[2] in 1705. In 1819, Laennec[3] correlated the clinical features of the disease with the observed pathological changes, and described the findings which make an accurate diagnosis possible during life.

Direct surgical attack upon the stenotic valve was suggested by Samways[4] in 1898, and by Brunton[5] in 1902. No further progress was made until Cutler's[6] method of transventricular section of the stenotic mitral valve opening was published in 1924. The amount of regurgitation produced, however, militated against its acceptance as a satisfactory technique. The following year, Souttar[7] successfully "dilated" a stenosed mitral valve, inserting the index finger through the left auricular appendage. Further clinical attempts to open a stenosed valve were unreported until Bailey presented his concept of separation of the fused valve leaflets along the lines of the obliterated commissures in 1948. This allowed surgical correction of the obstruction without the necessity of producing regurgitation. The first successful mitral commissurotomy was accomplished on June 10, 1948.[1] Independently of the American accomplish-

*Surgeon, Bailey Thoracic Clinic, and Hahnemann Hospital and Medical College, Philadelphia, Pa.

**Former Resident in Thoracic Surgery, Hahnemann Hospital and Medical College, and Trainee of the National Heart Institute. Presently, Chief, Department of Cardiovascular Surgery, Harrisburg Hospital and Harrisburg Polyclinic Hospital.

Presented at the Fifth International Congress on Diseases of the Chest, American College of Chest Physicians, Cologne, Germany, August 19-23, 1956.

ments, Brock,[8] in September, 1948, successfully carried out a commissural separation by digital pressure only.

Mitral Valvular Disease

Mitral Stenosis

All the corrective procedures for mitral stenosis were originally carried out through a left posterolateral thoracotomy. This approach afforded an easy means of digital exploration of the left cardiac chambers through the auricular appendage. Digital splitting of the anterior commissure was facilitated by counterpressure over the ventricular wall. Auricular appendectomy was accomplished routinely, hoping to prevent further hazard from emboli. The concept of temporary occlusion of the carotid flow during interatrial manipulations was proposed by Bailey et al.[9] to prevent cerebral embolization. This was done by passing umbilical tapes around the innominate and the left common carotid arteries at their origin from the aortic arch.

Although the operation of mitral commissurotomy as performed from

FIGURE 1A FIGURE 1B FIGURE 1C

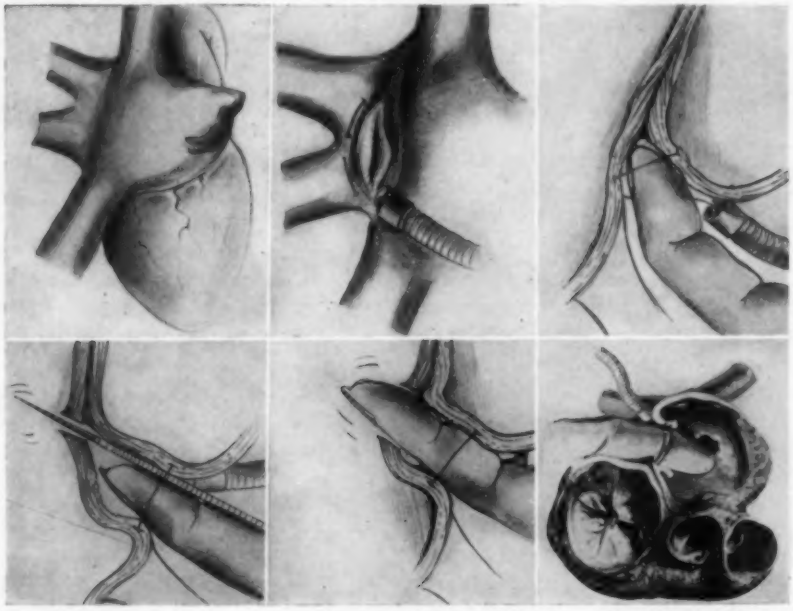


FIGURE 1D FIGURE 1E FIGURE 1F

Figure 1: Technique for the right-sided approach for mitral commissurotomy.—*Figure 1A:* The relationship of the right pulmonary veins to the vena cavae is demonstrated, viewing the heart from the right side.—*Figure 1B:* The interatrial groove, anterior to the pulmonary veins, and posterior to the right atrium is dissected. The purse string suture is shown.—*Figure 1C:* The interatrial groove is deepened by blunt finger dissection.—*Figure 1D* and *E:* Entry into the left atrium through the reflection of the septum.—*Figure 1F:* Commissurotomy is accomplished by digital or instrumental technique.

TABLE I
MITRAL COMMISSUROTOMY-COMPARISON OF COMMISSURAL OPENING IN RIGHT AND LEFT-SIDED APPROACH

	Right-Sided Approach Per Cent	Left-Sided Approach Per Cent
Both Commissures Opened	97.3	33.1
Only One Commissure Opened		
Anterior	1.6	65.0
Posterior	1.1	1.9
	100	100

the left side was becoming more widely accepted, its shortcomings were also recognized. Adequate digital and instrumental opening of the posteromedial commissure was seldom obtained. Since mobilization of the valve leaflets was only partially accomplished, it is quite probable that this group of patients eventually will show a higher incidence of recurrent valvular obstruction or re-stenosis.[10]

A right-sided approach to the mitral valve was first presented by Neptune and Bailey,[11, 12] in 1954. The ease with which posteromedial commissurotomy could be carried out by this approach stimulated its clinical use. Improvements in technique have led to its adoption for routine commissurotomy. This approach has now been used in more than 200 cases of mitral stenosis[13] (Figure 1).

There are many advantages to the right-sided as compared with the left-sided approach. More adequate mobilization of the anterior and posterior commissures is attained by this method (Tables I and II).

Coexisting tricuspid and aortic valvular pathology may be treated during the same operative procedure. During anesthesia, the supine position is tolerated more readily than the left lateral position. The incidence of hypotension and diminished cardiac output has been greatly averted with the supine position.[14] The presence of an unrecognized coexisting interatrial septal defect may be diagnosed and treated by atrio-septo-pexy. The submammary incision used in this approach produces less pain and shoulder dysfunction and is shorter and cosmetically more acceptable. Interatrial thrombi, when encountered, are carefully avoided. When atrial thrombi are encountered during surgery, postoperative anti-coagulants are utilized until such a period has elapsed that organization and fixation of the thrombus seems certain and further propagation is obviated. Although protection of the cerebral vessels is not carried out, the incidence of operative embolization remains low (Table III). In comparing the two approaches, the over-all operative mortality presents no difference of statistical significance (Table IV).

There are some problems encountered in the right-sided approach. Change in position of the patient produces a different anatomical commissural approach. This must be carefully noted before attempts at commissurotomy are carried out. Closure of the left atrium is slightly more diffi-

cult because of the absence of an appendage. With further experience, this has not posed a serious handicap.

Mitral Insufficiency

Our initial attempts at correction of mitral insufficiency or regurgitation were universally unacceptable because of a prohibitive mortality rate, varying between 20 and 40 per cent.[12] Subvalvular slings in the form of pericardial tubes and vein grafts were used as the first procedure. Direct valvular suture was attempted, but these invariably pulled through due to the constant motion of the valve leaflets. Baffle plates of living tissue and plastics also failed. All methods of repair ultimately proved unsatisfactory. The concept of annular constriction was introduced by Davila et al.[15] Although the authors admit that the procedure is technically difficult, early results suggest diminution in the leak. The operative procedure of polar cross plication of the mitral annulus, as reported by Henry T. Nichols,[16] one of the surgeons at our Clinic, is at present giving the best results in repair of mitral insufficiency. The success of this operation is

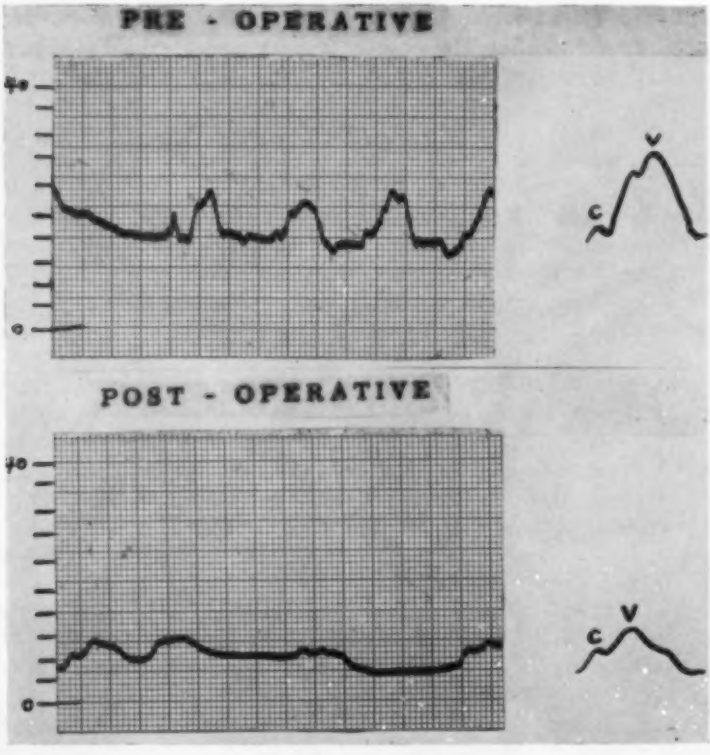


FIGURE 2: Left atrial pressure tracing in mitral insufficiency. The mean left atrial pressure is elevated. A large C-V wave is demonstrated. Its absence is noted in the post-operative pressure tracing.

TABLE II

MITRAL COMMISSUROTOMY COMPARISON OF VALVE SIZE ATTAINED BY SURGERY

Valve Size	Right-Sided Approach Per Cent	Left-Sided Approach Per Cent
Over 2 Finger Opening (More than 4 cm.²)	3.0	2.0
2 Finger Opening	66.5	43.0
1½ Finger Size (2.5-3.9 cm.)	28.0	46.0
Less than 1½ Finger Opening	2.5	2.0
Valve Size Unrecorded	0	7.0
	100	100

dependent upon several basic principles. The annulus of the valve is the only structure which is strong enough to hold sutures under great tension.

Experimental studies on dogs indicate that actual fibrous fusion occurs where the plication has brought the two points of the annulus into apposition.[17] The evaluation of these patients has included pre and postoperative left heart catheterization and cardiac ventriculography. The preoperative left atrial tracings showed a ventricularization pattern,[18] with absence of this finding in the postoperative study. Seventy per cent diodrast injection into the left ventricle in the presence of mitral regurgitation resulted in opacification of the left atrial chamber[19] (Figure 3). This type of radiographic study has been carried out in 82 patients without mortality. Postoperative studies from 10 days to three months later show little evidence of insufficiency when the surgeon considered the plication adequate.[20]

When mitral stenosis and major insufficiency coexist, the stenosis is corrected first, utilizing the left-sided approach. Mitral annulus plication is then carried out simultaneously, when indicated.

Aortic Valvular Disease

Aortic Stenosis

The first surgical attempt at the correction of aortic stenosis was that of Tuffier[21] in 1913. He invaginated the anterior wall of the aorta and dilated the valve digitally without entering the lumen of the vessel. The first successful aortic commissurotomy was done on June 22, 1950 by Bailey,[12] passing a now obsolete dilator through the valve from the ventricular approach. Only a limited dilatation was accomplished. An improved Donaldson tri-radiate dilator was developed and first used in 1952. Transventricular aortic commissurotomy is essentially a blind procedure. With this technique, it is suspected that an accurate commissural separation was not always obtained. The myocardial insult from the incision frequently resulted in serious cardiac arrhythmias.

In order to circumvent these problems, transaortic commissurotomy was developed. This procedure allows digital palpation of the valve through

an artificially created pouch attached to the ascending aorta just above the valve. Commissurotomy may then be carried out under digital guidance. The commissures may then be separated by digital pressure, incision, dilatation, or by a combination of these modalities. Although this method represented a distinct advance, it did not always permit the surgeon to correct the stenosis when severe structural abnormalities of the valve are found. Extreme calcification and rigidity of the leaflets may preclude adequate mobilization of the obstructed valve in some cases. Accordingly, with recent development of practical equipment for heart-lung bypass, extracorporeal oxygenation of the blood, and the perfection of methods for the performance of surgery within the heart under direct vision, it was logical to apply such techniques to the correction of aortic stenosis.

From April 1952 to February 1956 the Bailey Thoracic Clinic treated 287 patients with aortic stenosis by closed heart techniques. One hundred and nine of them had associated mitral stenosis (Table IV). Ventricular fibrillation was the main cause of death in patients operated for pure aortic stenosis. When the results of transventricular and transaortic routes are compared (Table IV), our experience seems to indicate that the combination of mitral with aortic stenosis results in a better prognosis than when the patient has surgical correction of isolated aortic stenosis. The stenosed mitral valve apparently protects the left ventricle against the severe myocardial injury which is so characteristic of isolated aortic valvular disease. Fatal arrhythmias have not occurred in this combined group. At the present time, the transventricular approach is preferred for the surgical correction of this combination. More definitive surgical correction may have to be instituted at a later date. If physiological

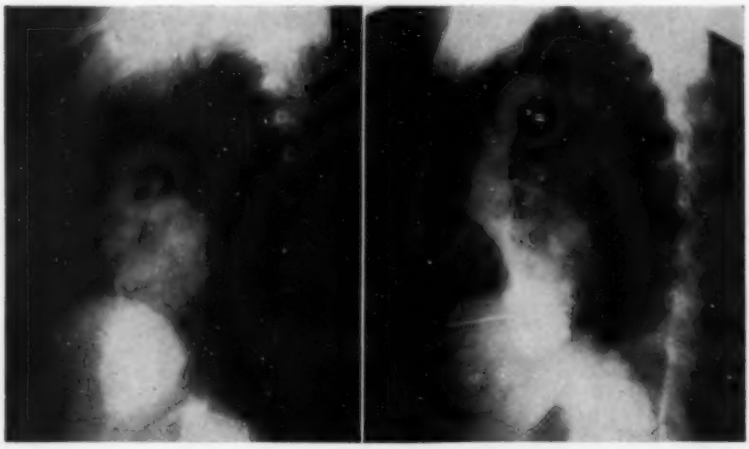


FIGURE 3: Preoperative and postoperative left ventriculography. The left x-ray shows massive regurgitation from the left ventricle into the left atrium. The x-ray on the right shows minimal mitral valve leak following a Nichols operation for the four plus insufficiency which was present.

studies indicate residual stenosis, this can be treated by open techniques.

Aortic stenosis is seldom of congenital origin. In some cases, the valve may be bicuspid or occasionally multicuspid. Dilatation of the funnel or megaphone type of aortic stenosis frequently produces some degree of aortic insufficiency. To avoid this end result, open heart surgery must be considered in all of the congenital cases. One often encounters a child with aortic stenosis of such severity that progressive myocardial degeneration is imminent. Under such circumstances, a transventricular approach may be the appropriate technique recommended as a temporizing procedure.

Our experience with open heart surgery includes 11 patients with aortic stenosis. The extracorporeal circulation was maintained by the Friedland-Gemeinhardt oxygenator for periods ranging from seven to 30 minutes. All except one survived. This death was due to ventricular fibrillation, not responding to defibrillatory measures. Retrograde perfusion of the coronary sinus was carried out as described by Blanco, Adam, and Fernandez[22] who observed that coronary circulation could be sustained, when the aorta was opened, by retrograde perfusion of the myocardial capillary bed by way of the coronary sinus.

TABLE III

OPERATIVE EMBOLIZATION INCIDENTAL TO MITRAL COMMISSUROTOMY FROM THE RIGHT—210 CASES

Patient	Procedure	Clot In Atrium	Calcification In Leaflets	To	Outcome
P. R.	Mitral comm., aortic explored	Large, soft granular	Posterior commissure and septal leaflet	Brain	Survived with alexia and agraphia only
L. G.	Mitral comm., tricuspid comm.	3 cm. in diameter above ant. comm.	Moderate	Aortic bifurcation	Survived. Removed at same operation, no complications
M. L.	Mitral (re-operation), tricuspid explored	Large, soft	Slight	Mid-brain	Survived. Complete relief with con. caudal block only—3 days
W. B.	Mitral comm., tricuspid explored	Numerous small vegetation-like clots	Moderate	Right femoral artery	Died 24 hrs. Spastic biplegia. No recovery
M. M.	Mitral comm.	None	Embolous believed of calcific origin, Periorificial nodular calcification located diffusely around all edges of both leaflets and commissures. Felt to be loose during surgery	Brain	Hemiplegia

Aortic Insufficiency

The clinical and objective evidences of disability are almost directly proportional to the diastolic regurgitant flow, regardless of the etiology. Luetic aortitis is associated with a generalized dilatation of the aortic annulus fibrosus, due to necrosis and weakening of the ring. This type of valvular pathology has been treated clinically by a surgical procedure designed to constrict the annulus below the coronary ostia.[23] Clinically, this has been discarded because of an operative mortality of 30 per cent. In addition, the annulus wrap was observed to migrate toward the apex of the heart, slipping off the annulus and failing to help the insufficiency.

More recently, external plication of the base of the aorta and the annulus fibrosus was carried out, placing this plication in the area of the non-coronary-bearing aortic cusp. Suture of the aorta and annulus is facili-

TABLE IV

TABULATION OF 2012 CASES OF CARDIAC SURGERY FOR ACQUIRED VALVULAR DISEASES

Group	Valvular Pathology	Approach	Number of Cases	Number of Operative Deaths	Operative Mortality Rate Per Cent
I	Mitral stenosis, pure, or with insignificant insufficiency	L	1051	79	7.5
		R	210	14	6.7
II	Aortic stenosis, pure, or with insignificant insufficiency	L	93	25	26.9
		R	88	14	15.9
	Open heart technique—	Open bilateral	11	1	9.1
III	Aortic stenosis, and mitral stenosis, pure	L	21	0	0
		R	4	0	0
IV	Aortic stenosis, and mitral stenosis with minor insufficiency associated	L	64	15	23.4
		R	20	2	10.0
V	Major aortic stenosis and insufficiency. (Treated by aortic commissurotomy only)	L	7	4	57.1
		R	9	1	11.1
VI	Mitral insufficiency Nichols operation	L	48	7	14.6
VII	Mitral insufficiency— operations other than Nichols	L	170	67	25.4
VIII	Major mitral stenosis and insufficiency. (Treated by mitral commissurotomy only)	L	115	21	18.3
		R	32	5	15.6
IX	Mitral stenosis plus multi-valvular lesions	R	58	17	29.3
X	Lutembacher's syndrome	R	8	1	12.5
XI	Mitral stenosis, interatrial septal defect and anomalous pulmonary venous drainage of right lung	R	1	0	0

tated by use of a fenestrated aortic insufficiency clamp.[24] Complete correction by this closed technique has not yet been accomplished. While there are shortcomings in this technique, the current experimental work would indicate that these shortcomings could be obviated.

Aortic insufficiency of rheumatic origin has been considered to exist only in association with some degree of aortic stenosis. Most cases have heavy valvular calcification to compound the problem. Aortic prosthetic valves of many types have been tried; results to date are unsatisfactory. Our experiences with the prosthetic ball valve in the descending aorta have been equally as discouraging as those of Hufnagel.[25] His initial operative mortality of 40 per cent has now been reduced to 26 per cent.

With open heart surgery, it is anticipated that some of these problems can be handled more easily. Certainly, visual division of the commissure should prevent the creation of additional leak due to misplaced or too vigorous commissurotomy.

Tricuspid Valvular Disease

Tricuspid Stenosis

Tricuspid stenosis of rheumatic origin occurs only in the presence of mitral valvular disease. Although Reale et al[26] have described well the physiological findings which are characteristic of its presence, in practice significant tricuspid disease can be recognized with certainty only by digital exploration at the time of surgery. Some degree of tricuspid stenosis was present in 22 per cent of those patients explored for mitral stenosis as the primary lesion. These patients were treated by mitral and tricuspid commissurotomy.

Tricuspid Insufficiency

This defect was found in 34 patients of the group of 175 rightsided mitral commissurotomies done for known mitral stenosis. Tricuspid annular plication was done in 2 patients with severe insufficiency. In several suspected cases of tricuspid incompetence, right cardiac ventriculography was carried out. Massive regurgitation of diodrast into the right atrium was demonstrated in these cases.[27]

Discussion

Our earlier experiences with patients submitted to surgery for diseased valves of rheumatic origin were usually those patients with single valvular lesions. Gradually, the patients referred to us became more complicated and it was necessary to devise methods or techniques applicable to a case needing two and oftentimes three valves operated upon.

By virtue of this need, we have devised a right thoracotomy approach through the third or fourth intercostal space with the patient in the supine position. This incision allows easy access to the mitral, aortic, and tricuspid valves for the relief of stenosis (Figure 1).

One thousand and fifty-one patients were operated upon from the left side for mitral stenosis. This group had either a "pure" mitral stenosis or stenosis with an associated mitral insufficiency of insignificant degree. The resulting operative mortality rate was 7.5 per cent (79 deaths in

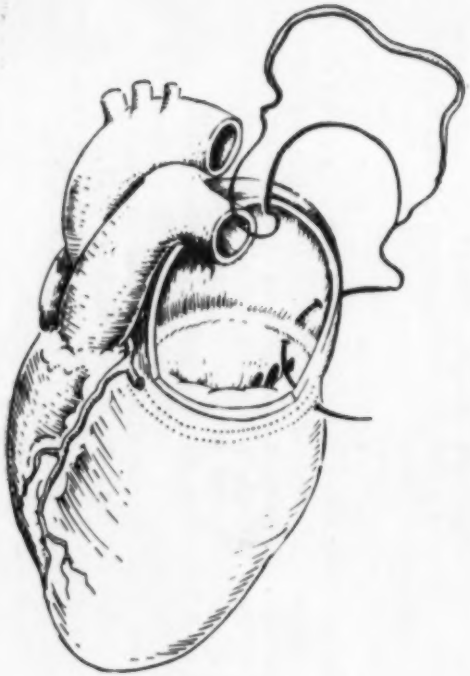


FIGURE 4A

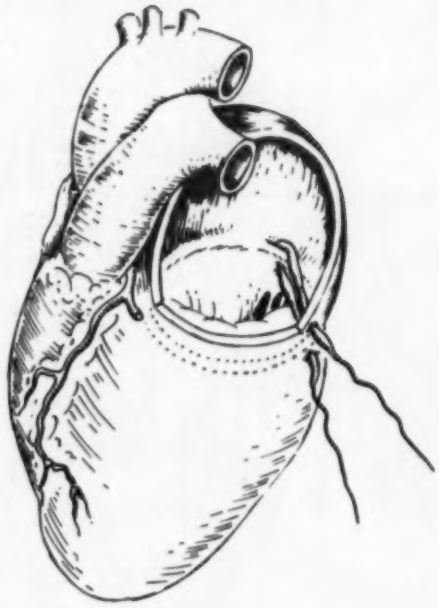


FIGURE 4B

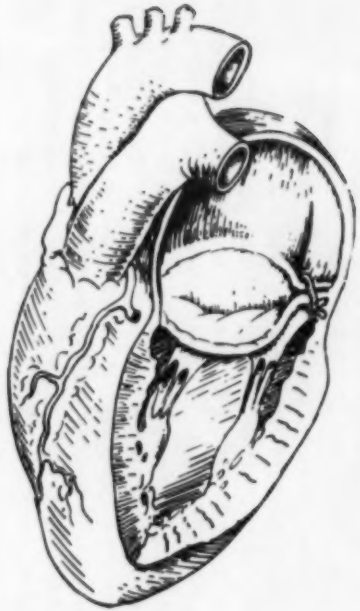


FIGURE 4C

Figure 4: Diagrammatic demonstration of the Nichols operation for mitral insufficiency.—*Figure 4A:* Double armed suture, central portion wrapped with pericardium, first needle passed around the mitral annulus.—*Figure 4B:* Suture in position, encircling the annulus at the posterior commissure.—*Figure 4C:* Suture tied down to approximate the edges of annulus, obliterating incompetence.

1,051 patients operated upon). By utilizing the right-sided approach to the mitral valve via the interatrial groove, the operative risk was reduced to 6.7 per cent (14 deaths in 210 patients operated using this technique) (Table V). These two groups were unselected and represented 1,261 consecutive patients and included all functional classifications (Table VI). There were other groups of patients who had mitral commissurotomy performed but had other associated lesions (Table IV). The operative risk in these latter categories is much greater.

The present technique of operating upon the stenotic mitral valve from the right side has resulted in a greater technical efficiency as reflected by the fact that both commissures were opened in 97.3 per cent of the cases (Table I). Such was the case in only 33.1 per cent of the patients operated from the left side. The opening or valvular orifice size obtained when the patient is operated from the right side has been significantly larger than in those operated from the left. Sixty-six and one half (66.5) per cent operated from the right obtained a two finger or larger opening, while only 43 per cent operated from the left side obtained a two finger (4 sq. cm.) or larger valve opening by commissurotomy (Table II).

These statistics show that the merits of the surgical correction of mitral stenosis are far superior from the right side as compared with the approach from the left.

The early operative procedures for mitral regurgitation include a variety of methods for the surgical correction of the insufficiency. The resulting operative risk of 25.4 per cent was prohibitive and such surgery was abandoned until the Nichols' operation was devised. Although the total number treated by the later technique has been small, the results at this early stage have been most encouraging. Seven operative deaths occurred in the first 48 patients treated by this technique, presenting a mortality rate of 14.6 per cent. This reduction in the operative risk, coupled with the marked decrease and in some cases obliteration of regurgitation, presents an entirely new perspective of a previously most discouraging valvular defect. The Nichols' procedure for mitral insufficiency has resulted in a reduction in the operative mortality of more than 50 per cent. The reduction or obliteration of the regurgitation through the mitral valve is determined by the palpating finger within the left atrium during surgery, and is substantiated by a reduction in heart size after surgery and further confirmed by cardiac catheterization and ventriculography (Figure 3).

The presence of an interatrial septal defect does not significantly alter the correction of a coexisting mitral stenosis (Lutembacher's syndrome). We have operated on eight such cases with only one death (Table IV). Another was found to have an interatrial septal defect, right anomalous pulmonary venous drainage, and mitral stenosis. Simultaneous correction of all the defects was possible with an uneventful recovery.

There have been 192 patients operated upon for aortic stenosis with or without an associated aortic insufficiency of physiologic insignificance (Table IV). These relatively pure stenotic lesions operated upon from the

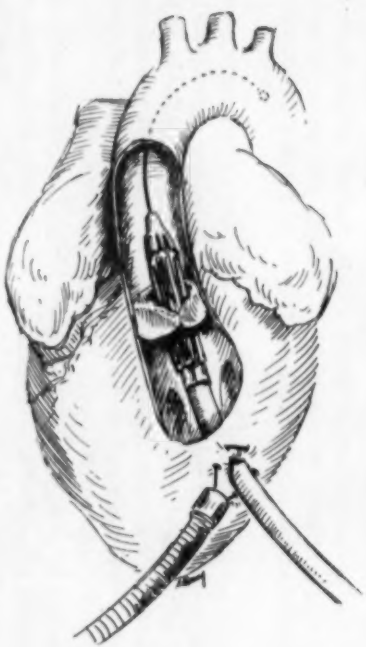


FIGURE 5A

FIGURE 5B

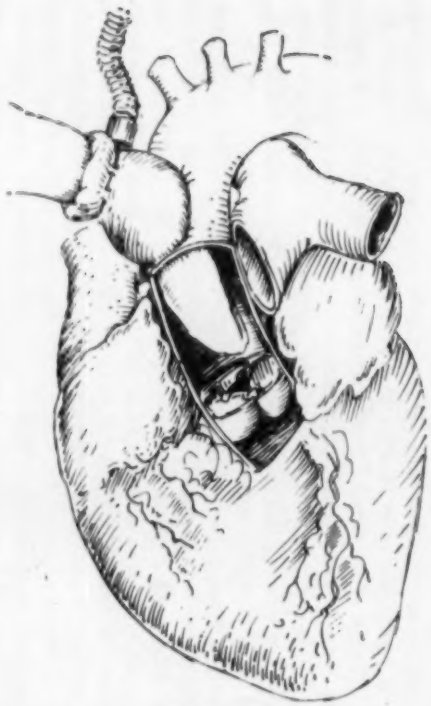


FIGURE 5C

Figure 5: Technique of aortic commissurotomy from the left-sided approach (transventricular).—*Figure 5A:* Aortic dilator in position.—*Figure 5B:* Aortic dilator expanded to separate the commissures of the stenotic valve.—*Figure 5C:* Aortic commissurotomy through right thoracotomy incision. A pericardial pouch is sutured to the aorta; the index finger is inserted into the aorta for exploration and commissurotomy.

left by the transventricular route resulted in the alarmingly high operative mortality rate of 26.9 per cent (25 deaths in 93 cases). By utilizing the right-sided transaortic approach to the valve, the risk was reduced to 15.9 per cent. Until such a time when we are able to institute prophylactic measures to obviate the occurrence of ventricular fibrillation during the transventricular approach, it would seem that the transaortic commissurotomy from the right side is the technique of choice between these two methods. Recently the risk appears to have been reduced further (one death in 11 patients, 9.1 per cent) by utilizing the "open" technique, performing commissurotomy under direct vision.

Late follow-up results of this series of patients who had aortic commissurotomy (28) revealed that 70 per cent were symptomatically improved. While the right-sided transaortic approach does reduce the operative risk, their postoperative improvement almost parallels those cases having had transventricular aortic commissurotomy. Over a four year period, there has been a late death incidence of 19.7 per cent. This high rate may be related to the fact that a high percentage of these patients were over 50 years of age at the time of surgery.

The best postoperative results were obtained in the combined aortic and mitral stenosis group. Twenty-five were included in this category. All but four of these operative procedures were done from the left approach. There was no operative mortality in either group. Only two late deaths occurred in these cases. These results indicate that the left approach is equally as safe as the right one when both valves are stenotic. In view of this experience, we are now utilizing the left-sided approach in the treatment of combined aortic and mitral stenosis.

The remaining patients in Table IV are those with dynamically significant insufficiency in either the mitral or aortic valve in combination with other valvular lesions. The immediate operative mortality is high. However, the late results appear promising when the valvular competence can be restored.

Restenosis of a mitral valve following commissurotomy has occurred in 17 patients previously operated by one of the three surgeons in our group. Eleven of them were reoperated upon and in each case the original surgeon was in attendance at the subsequent operation. This procedure was followed in order to be certain that the original postoperative state of the valve could be compared accurately with its present restenotic condition. There was no operative death in this group, and adequate opening was obtained by the second operation. Two of these patients were reoperated a third time, one by the senior author and one by another surgeon of our group. Six with known restenosis were confirmed at autopsy.

A number of other patients who had initial valvular surgery elsewhere have been reoperated for "recurrent stenosis" by our group. It has not been possible to evaluate these patients without precise knowledge of the condition of the valve after the initial operation. It is anticipated that an increased incidence of restenosis will occur when only one commissure was opened, or when less than adequate mobilization of the valve leaflets

was obtained. In caring for a patient having had a mitral commissurotomy, one must always be alert, for, if restenosis occurs, secondary surgery must be considered, even though its occurrence is extremely rare.

Long Term Follow-up — Mitral Commissurotomy Symptomatic Changes

A follow-up study of 200 patients who had mitral commissurotomy was done. The postoperative period of observation ranged between 5½ and 8 years. Dyspnea occurred in 190 patients preoperatively. Postoperatively, it was absent in 57, unchanged in 21, better in 41, much better in 66, and worse in 5 patients. The presence of or history of edema was noted in 119 patients prior to surgery. Postoperatively, this symptom was observed in 25 patients. Hemoptysis was recorded in 93 patients before surgery, and in only three patients after surgery. Fatigue was present in 178 patients in the group; its presence postoperatively was recorded in 37 patients.

Twenty-two patients now complain of symptoms which were not present preoperatively. These include 2 cases with edema and 1 patient with fatigue. Two patients developed epilepsy. The remainder complained of nervousness, insomnia, and palpitations. In the majority of this latter group, it was suspected that a psychosomatic factor was prominent.

Postoperative febrile episodes occurred in 26 patients; in 6 of these, the episode was recurrent. Ten of these patients were suspected of having rheumatic fever, the diagnosis being proven in 2 cases. Ten additional patients were considered as cases of "post-commissurotomy syndrome." Four cases had fever with no known or suspected cause. Subacute bacterial endocarditis was confirmed in 1 patient and suspected in another.

A history of preoperative embolization was obtained in 33 patients. Only 2 of these have had embolic episodes since commissurotomy. One patient with no preoperative embolic episode has had an incident subsequent to surgery.

TABLE V

FUNCTIONAL CLASSIFICATION OF PATIENTS, OPERATED FOR MITRAL STENOSIS, ACCORDING TO THE AMERICAN HEART ASSOCIATION; COMPARING THE RIGHT AND LEFT THORACOTOMY APPROACH TO THE MITRAL VALVE

AHA Class	Left Side	Operative Deaths	Late Deaths	Right Side	Operative Deaths	Late Deaths
		Per Cent			Per Cent	
1.	17	1	0	3	0	0
		5.9	0		0	0
2.	355	9	27	83	3	1
		2.5	7.6		3.6	1.2
3.	612	59	36	118	8	1
		9.6	5.9		6.8	
4.	67	10	13	6	3	2
		14.9	19.4		50	33.3
TOTAL	1051	79	76	210	14	4
		7.5	7.2		6.7	1.9

Seventeen patients have had pregnancies during the follow-up period. Two of these were primiparas and delivered full term babies with no difficulty. Fifteen of the patients had pregnancies preoperatively as well. Twelve of these delivered full term infants; 1 has borne 2 children since commissurotomy. One patient had an abortion at three months, but had no cardiac symptoms. One patient had a tubal pregnancy, requiring laparotomy. One patient in the group had the pregnancy terminated at four months of gestation for medical cardiac reasons.

Objective Findings

The systemic blood pressure showed no change postoperatively in 186 patients. Fourteen now have some degree of hypertension. The cardiac rhythm showed no change in 180 patients. Nine cases with normal sinus rhythm have now converted to atrial fibrillation. Ten cases have now converted to paroxysmal atrial fibrillation. One patient having atrial fibrillation preoperatively has now been converted to normal sinus rhythm.

The heart sounds remained unchanged in 141 patients. The first mitral sound was normal or not as sharp in 54 patients. It was diminished because of mitral insufficiency in 5 patients. Mitral systolic murmurs remained unchanged in 119 patients. Seventy patients without systolic murmur developed a murmur after commissurotomy. Five patients with preoperative murmur had a louder murmur postoperatively. Six patients with a preoperative murmur now have no evidence of residual systolic murmur. Mitral diastolic murmurs remained unchanged in 150 patients. The murmur was absent in 21, decreased in 28, and louder in 1 patient. Twenty-six patients developed basal murmurs suggestive of aortic valvular disease.

Heart size remained unaltered in 142 patients. The heart size was

TABLE VI

OPERATIVE RISK SHOWING COMPARISON OF RIGHT AND LEFT THORACOTOMY APPROACH TO THE MITRAL VALVE FOR CORRECTION OF MITRAL STENOSIS

	Approach to Mitral Valve	Number of Cases	Number	Operative Mortality Rate Per Cent	Late Deaths	Late Deaths Per Cent
Pure MS or associated insignificant valve lesions	Left thoracotomy approach	1051	79	7.5	76	7.2
Pure MS or associated insignificant valve lesions	Right thoracotomy approach	210	14	6.7	4	1.9
	TOTAL	1261	93	7.4	80	6.3

smaller in 29 patients, 24 of these showing significant decrease. The heart size was larger in 29 patients, 18 of these demonstrating significant increase. The American Heart Classification remains unchanged in 79 patients. One hundred and thirteen patients were moved into a better functional class by commissurotomy. Eight unimproved patients showed more limitation in their activities.

In the patients' self-evaluation, 48 consider themselves cured; 110 classify themselves as improved, 63 of these markedly improved; 4 are questionably better; and 9 patients are worse.

SUMMARY

Our experiences in the operative treatment of more than 2,000 patients with acquired valvular disease are presented. Recent modifications in surgical technique are described and their advantages outlined.

1. More adequate mobilization of the mitral valve leaflets has been attained when commissurotomy is done from the right thoracic approach. A bicommissural opening was attained in 97 per cent of those patients operated by the right sided approach, and only in 33 per cent of those explored through the left side.

2. Cross-polar plication of the valve annulus, as proposed by Nichols, provides effective relief of mitral regurgitation with a reduction in the mortality rate to 14 per cent.

3. A five and one-half to eight year follow-up was obtained in 200 mitral commissurotomies, and their present status reported.

4. The indications and the techniques for aortic commissurotomy are presented with a discussion of our results by the open technique.

RESUMEN

Se presenta nuestra experiencia del tratamiento operatorio en más de 2,000 enfermos con enfermedad valvular adquirida. Se describen las recientes modificaciones de la técnica quirúrgica y se señalan sus ventajas.

1. Se ha obtenido una movilización de las hojillas de la válvula mitral cuando la comisurotomía se ha hecho por la vía torácica derecha.

Se obtuvo una abertura bi-comisural en 97 por ciento de los enfermos operados por el lado derecho y sólo 33 por ciento en aquellos operados por el lado izquierdo.

2. La plegadura crucial-polar del anillo valvular, como se propuso por Nicholas, da alivio efectivo de la regurgitación mitral con una reducción de la mortalidad a 14 por ciento.

3. Se logró un seguimiento de los enfermos de cinco y medio a ocho años en 200 enfermos y se refiere su condicion actual.

4. Las indicaciones y las técnicas para la comisurotomía aórtica se presentan con una discusión de nuestros resultados por la técnica abierta.

RESUME

Les auteurs présentent leur expérience du traitement chirurgical de plus de 2,000 malades, atteints d'affection valvulaire acquise. Ils décrivent de

récentes modifications de la technique chirurgicale et insistent sur leurs avantages:

1. Ils ont obtenu une mobilisation mieux adaptée des valves de la mitrale, quand la commissurotomie a été pratiquée en abordant par le côte droit du thorax. Une ouverture bicommissurale fut possible chez 97% de ces malades opérés para le côté droit, es seulement chez 33% de ceux opérés par le côté gauche.

2. Une plication de la valve annulaire, comme elle a été proposée par Nichols, permet un soulagement efficace de la régurgitation mitrale, avec une réduction du taux de mortalité de 14%.

3. Les auteurs ont pu suivre 200 commissurotomies mitrales de 5 ans et demi à 8 ans, après l'intervention et ils exposent l'état actuel des malades.

4. Ils décrivent les indications et les techniques de la commissurotomie aortique, en discutant les résultats qu'ils ont obtenu en opérant à coeur ouvert.

ZUSAMMENFASSUNG

Es werden unsere Erfahrungen vorgelegt bei der operativen Behandlung an mehr als 2000 Patienten mit erworbener Gefässerkrankung. Jüngste Modifikationen der chirurgischen Technik werden beschrieben und ihre Vorzüge umrissen.

1. Es wurde eine adequate Mobilisation der Mitralklappensegel erzielt, wenn die Commissurotomie von der rechten Thoraxseite aus vorgenommen wurde. Eine Eröffnung beider Commissuren wurde bei 97% solcher Patienten erzielt, die von einem rechtsseitigen Zugang aus operiert wurden gegenüber nur 33% bei denjenigen, die von der linken Thoraxseite aus angegangen wurden.

2. Eine Faltung des Klappenringes mit gekreuzten Polen nach dem Vorschlag von Nichols gewährt effektive Beseitigung des mitralen Rückstromes mit einer Herabsetzung der Sterblichkeitsziffer auf 14%.

3. Eine sich über 5½ bis 8 Jahre erstreckende Nachkontrolle wurde bei 200 Fällen von mitralen Commissurotomien erreichts, und über ihren gegenwärtigen Befund wird berichtet.

4. Die Indikation und die Technik der Aorten-Commissurotomien werden beschrieben nebst einer Diskussion unserer Resultate mit der offenen Technik.

REFERENCES

1 Bailey, C. P.: "The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy)," *Dis. Chest*, 15:377, 1949.

2 de Vieussens, R. in Garrison, F. H.: *An Introduction to the History of Medicine*, Philadelphia, W. B. Saunders Company, 1929, p. 250.

3 Laennec, R.: *Traite de l'Auscultation Mediate*, Paris, 1819. (Translated by John Forbes, 1823).

4 Samways, D. W.: "Cardiac Peristalsis, Its Nature and Effects," *Lancet*, 1:927, 1898.

5 Brunton, L.: "Possibility of Treating Mitral Stenosis by Surgical Methods," *Lancet*, 1:352 and 547, 1902.

6 Cutler, E. C., Levine, S. A. and Beck, C. S.: "Surgical Treatment of Mitral Stenosis," *Arch. Surg.*, 9:689, 1924.

7 Souttar, H. S.: "Surgical Treatment of Mitral Stenosis," *Brit. M. J.*, 2:603, 1925.

8 Brock, R. C., Baker, C. and Campbell, M.: "Valvulotomy for Mitral Stenosis, Report of Six Successful Cases," *Brit. M. J.*, 1:1283, 1950.

9 Bolton, H. E., Delmonico, J. E., Jr. and Bailey, C. P.: "Prevention of Cerebral Embolism During Mitral Commissurotomy," *Ann. Int. Med.*, 41:272, 1954.

10 Bailey, C. P. and Goldberg, H.: "Recurrent Mitral Stenosis—Diagnosis by Simultaneous Left and Right Heart Catheterization." (To be published.)

11 Neptune, W. B. and Bailey, C. P.: "Mitral Commissurotomy Through the Right Thoracic Approach," *J. Thoracic Surg.*, 28:15, 1954.

12 Bailey, C. P.: *Surgery of the Heart*, Philadelphia, Pa., Lea & Febiger, 1955, p. 623.

13 Bailey, C. P. and Morse, D. P.: "Mitral Commissurotomy Performed from the Right Side," *J. Thoracic Surg.*, to be published.

14 Keown, K. K.: *Anesthesia for Cardiac Surgical Patient.* (In press.)

15 Davila, J. C., Mattson, W. W., Jr., O'Neill, T. J. R. and Glover, R. P.: "A Method for the Surgical Correction of Mitral Insufficiency," *Surg., Gynec. and Obst.*, 98: 407, 1954.

16 Nichols, H. T.: "Polar Cross Plication of the Mitral Annulus," Presented at Meeting Amer. Ass'n. for Thoracic Surgery, Miami, Florida, May 1956.

17 Gilman, R. A., Musser, B. G., Imbriglia, J. E., Vasquez, M. J. and Nichols, H. T.: *Experimental Study of the Fusion of the Mitral Annulus at the Site of Polar Cross Plication in Dogs.* (To be published.)

18 Musser, B. G., Bougas, J. and Goldberg, H.: "Left Heart Catheterization, Physiological Studies in Mitral and Aortic Valvular Disease," *Am. Heart J.*, 52:567, 1956.

19 Lehman, J. S., Musser, B. G. and Lykens, H.: "Cardiac Ventriculography," *Am. Jrnl. Roentgenology, Radium Therapy, and Nuclear Medicine*, 77:207, 1957.

20 Musser, B. G., Lehman, J. S., Morse, D. P. and Gilman, R. A.: "The Evaluation of Mitral Regurgitation by Cardiac Ventriculography," (To be published.)

21 Tuffier, T.: "Etat actuel de la chirurgie intrathoracique," Trans. Internat. Cong. Med., London, 1913; Sect. 7, Surg. Part 2, p. 249, 1914.

22 Blanco, D., Adam, A. and Fernandez, A.: "A Direct Experimental Approach to the Aortic Valve. II. Acute Retrograde Perfusion of Coronary Sinus," *J. Thoracic Surg.*, to be published.

23 Bailey, C. P. and Likoff, W.: "Surgical Treatment of Aortic Insufficiency," Presented at 35th Annual Meeting American College of Physicians, Chicago, Illinois, April 7, 1954.

24 Bailey, C. P. and Musser, B. G.: "Fenestrated Cardiovascular Clamps," (To be published.)

25 Hufnagel, C. A., Harvey, W. P., Rabil, P. J. and McDermott, T. F.: "Surgical Correction of Aortic Insufficiency," *Surgery*, 35:673, 1954.

26 Reale, A., Goldberg, H., Denton, C. and Likoff, W.: "Rheumatic Tricuspid Stenosis. A Clinical and Physiological Study with a Suggested Method of Diagnosis," *Am. J. Med.*, to be published.

27 Musser, B. G., Lehman, J. S. and Gilman, R. A.: "Tricuspid Regurgitation, Its Diagnosis by Right Ventriculography," (To be published.)

28 Bailey, C. P. and Likoff, W.: "Surgical Management of Aortic Stenosis: An Evaluation of Techniques and Results," *Arch. Int. Med.*, to be published.

Pulmonary Changes in Collagen Diseases

J. F. KUZMA, M.D.
Milwaukee, Wisconsin

Introduction

In recent years there has been a great deal of interest expressed in a group of disorders referred to as "collagen diseases." This group has been more or less separated from others by virtue of the fact that the primary anatomic change takes place in the mesodermal structural units of the body rather than in epithelial parenchyma as is the case in so many well known human afflictions.[1, 2] The designation of collagen disease has received general approval especially by the clinician, however, its shortcomings have been disturbing to many others.[2, 3, 4] Admittedly it may foster rather careless thinking and unjustified grouping of poorly understood diseases but the serious objection lies in the fact that it does not identify the cause or fundamental nature of the disorder nor does it designate an anatomic site. Be that as it may it has served its purpose in focusing attention on heretofore unappreciated chemical and anatomic changes of supporting tissue ground substances.

The fundamental disturbance in collagen diseases is an alteration of the mucopolysaccharide ground substance of mesodermal tissue.[5] Histologically this is initially identified by tinctorial alterations, swelling, necrosis, disorganization, and followed almost immediately by inflammatory cellular proliferation and subsequently by repair. Changes affect the entire body for connective tissue and blood vessels are universal and do not form a collected mass or organ.

The anatomic site of maximum change, degree of change, and the speed of the development of the change have allowed a separation of collagen diseases at least on clinical grounds. Histologically there is no consistent difference which might allow diagnosis of a particular disease in this group by examination of lung alone. The commonly accepted conditions include acute disseminated lupus erythematosus, rheumatic fever, polyarteritis, rheumatoid arthritis, dermatomyositis, and scleroderma. Some are willing to also include serum sickness and glomerulonephritis. Table I shows the listing of anatomic sites of principal involvement and it can readily be seen that all of these diseases are actually general body disorders. In addition to major anatomic site there is also a consideration of speed of reaction and this is tabulated in Table II.

In these conditions the initial precipitation of acid mucopolysaccharides is followed by cellular reaction. Both of these changes may be dampened or inhibited by the antiphlogistic action of steroid hormones which in favorable cases leads to amelioration of symptoms, induces remissions or lessens sequelae.

Presented at the Annual Meeting, Wisconsin Chapter, American College of Chest Physicians, April 29, 1956.

The question of etiology apparently has no one answer at this time; just as in the field of cancer a single cause has not yet been identified. However, there are many reactions which can produce similar anatomic results. Certainly the anatomic changes attending antigen antibody reaction in fixed tissue may well explain the cause in a number of these disorders.[6] However, such has not been completely demonstrated nor has the proposed theory found acceptance by all. Figure 1 shows the phenomenon of precipitation of protein (albumin) by unrelated means. The degree of precipitation varies but the *phenomenon of precipitation* is accomplished in all. These represent precipitation of protein by heat, acids, salts, and heavy metals. Presumably precipitation of mucopolysaccharides within tissue may also have different "causes."

Review of Histologic Change

Pictorial demonstration of collagen disease change may be seen in the illustrations which are presented. Figure 2 shows stages of precipitation of mucopolysaccharides in connective tissue. The left portion of the photograph shows a loose connective tissue with considerable intercellular ground substance. In the central portion one sees the development of vacuoles and some swelling and separation of the delicate fibriles; whereas in the right portion of the photograph there is actual precipitation and appearance of granular density. This may take place in any part of the body. Figure 3 shows such development within a blood vessel wall. In the two vessels of the left half of the photograph are portions of elastic lamina which have largely disappeared and are replaced by a swollen edematous vacuolated tissue. In the right half of the photograph the cellular inflammatory response which follows such breakdown of connective tissue can be seen in a very early stage. Advanced tissue breakdown leads to the pattern of Figure 4 which is experimental polyarteritis. The thick swollen vessel reveals a wide dark zone outlining the collapsed narrow lumen. Since this zone of tissue breakdown is non-cellular, has

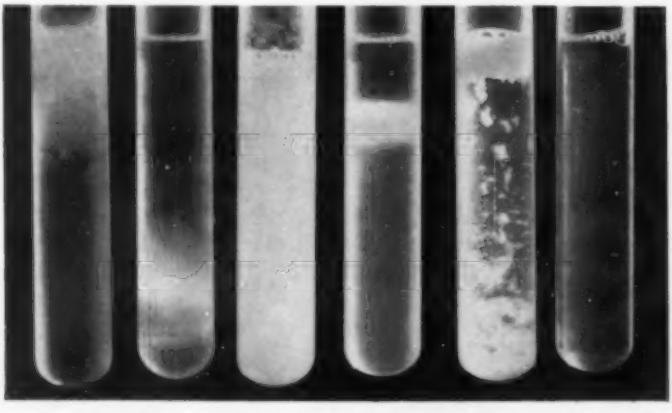


FIGURE 1

TABLE I
MAJOR ANATOMIC INVOLVEMENT

	Acute Lupus	"Serum" Sickness	Rheumatic Fever	Polyarteritis	Rheumatoid Arthritis	Dermatomyositis	Scleroderma
Skin	++++	++	+	+++	+	+++	++++
Subcutaneous tissue	++	+	++++	+++	++++	++++	+++
Joints	++	++++	++++	++	++++	++	++
Serosal surfaces	+++	±	+++	+	±	+	++
Blood vessels	+++	++	+++	++++	+	++	++++
Heart	+++	±	++++	++	+	++	++
Kidneys	++++	±	±	+++	±	±	+++
Spleen	+++	±	±	+	±	±	+
Lungs	+++	+	++++	++++	+	++	+++

TABLE II
TEMPO OF ANATOMIC CHANGE

	Acute Lupus	"Serum" Sickness	Rheumatic Fever	Polyarteritis	Rheumatoid Arthritis	Dermatomyositis	Scleroderma
Acute edema swelling fibrinoid necrosis inflammatory reaction	++++	++++	++	+++	+	+	±
Subacute large necrosis histiocytic reactions thrombosis angiitis granulations	+	±	++++	++++	++++	+++	+
Chronic atrophy of tissue fibrous replacement sclerosis-hyalinization	+	—	(heart) ++++	++	++++	++++	++++

a greater affinity for eosin and appears granular and smudgy, it is referred to as fibrinoid necrosis. Figure 5 shows the end stage of changes which were initially comparable to those of the right side of Figure 2. Now there is condensation, increased density, widening and stiffening of the fibers, and decreased cellularity of tissue which has been so affected. Since this end stage sclerosis is particularly related to vessels, narrowing and hyalinization of vessels may lead to severe parenchymal disturbance of various organs as a late manifestation.

Pulmonary Findings

If one studies such changes to the lung they may be observed in the pulmonary vessels, in the interstitial supporting tissue, and in the bronchial tree. In these areas general considerations of collagen breakdown apply. However, similar change taking place in the alveolar septa produces additional features which might preferably be demonstrated and referred to as the *pulmonary alterations of collagen diseases.* The following descriptions are a composite picture as interpreted by the author chiefly from personally studied cases and supported by literature review.[7-17] It is hoped that this description of changes may assist the clinician in his interpretations and studies of pulmonary symptoms observed in patients suffering from collagen diseases. It should be empha-

FIG. 2

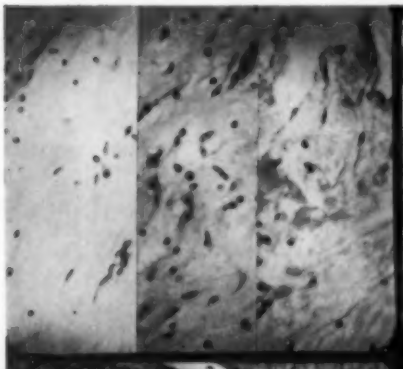


FIG. 3

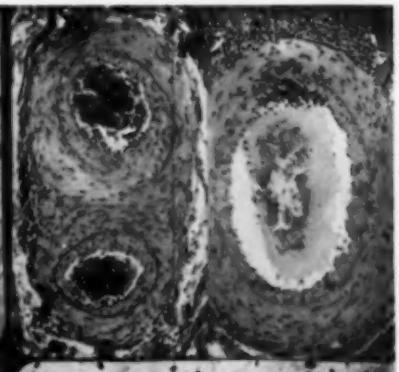


FIG. 4

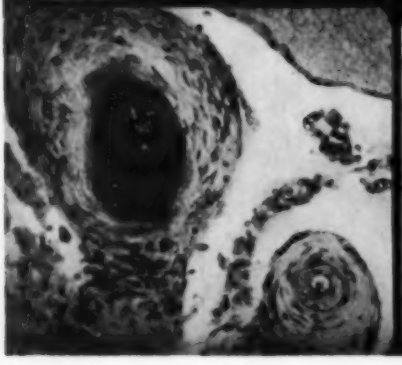
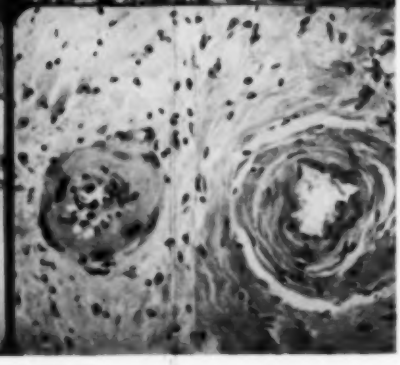


FIG. 5



sized that the changes are spotty in the lung, exacerbations and remissions occur and areas of disease do not all progress at the same rate or to the same degree. In Figure 6 one sees a portion of the lung with evidence of protein material and a few red blood cells in the alveolar spaces. The alveolar walls show various foci in which there is widening and increased cellularity. These areas are bright red in hematoxylin-eosin preparations and constitute points of fibrinoid necrosis. Figure 7 shows one of these areas under higher magnification and the disruption of the alveolar wall, its widening, smudginess, cellular reaction, and the evidence of leakage are readily observed. Such a change is shortly followed by rather severe proliferation of the alveolar lining cells and organization of fibrin exudate within the alveolar spaces. This produces a rather dense cellular "carnified" lung as seen in Figure 8. The organization of fibrinoid necrosis of alveolar walls is at times attended by large histiocytic cells, some of which are multinucleated and occasionally suggest features of an Aschoff's nodule. In this stage of the disease the gross appearance of the lung is one of mottled hemorrhages, considerable increase of consistency, and very fine granularity. The stage of change varies remarkably from zone to zone of involvement, some are hemorrhages and exudation, others organization and repair (Figure 9).

FIG. 6

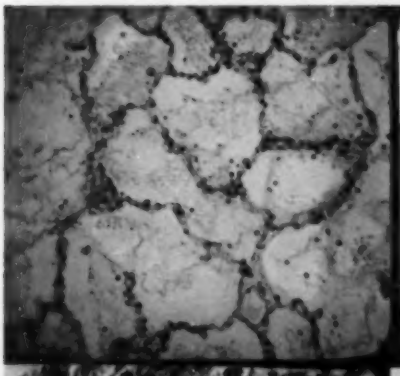


FIG. 7

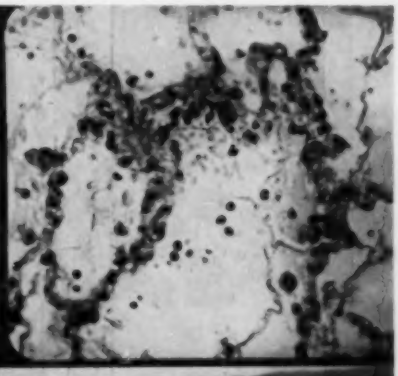


FIG. 8

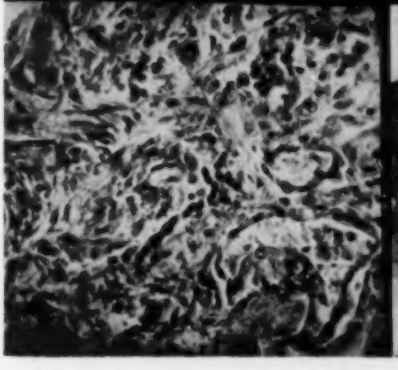


FIG. 9

In a matter of many days or weeks the process undergoes resolution and at that time there is condensation of the ground substance of involved areas and accentuation of all connective tissue zones which have been involved. The inflammatory cellular response gradually disappears and a marked thickening of the alveolar walls can be observed as in Figure 10. Eventually there is a rather dense alveolar wall pattern outlining very irregular air spaces as seen in Figure 11. The breakdown of alveolar septa and the formation of irregular air cells leads to the formation of a lung as pictured in Figure 12 in which early cyst formation is identified in a rather dense fibrous organizing background of lung tissue. In Figure 13 this is the extreme pattern of cystic changes of the lung without bullous formations of the pleura.

The speed with which such changes take place and the amount of lung tissue involved varies in the different diseases (Table II). Acute rheumatic fever, lupus erythematosus and polyarteritis are more often characterized by the acute and subacute patterns; while in rheumatoid arthritis, dermatomyositis, and especially scleroderma the progress of the change takes place much more slowly and the early stages of fibrinoid necrosis are frequently not significant. As such diseases have recurrences and exacerbations much of the lung may eventuallly become involved leading to an indurated rubbery dark hypocrepitant lung (rheumatic fever, disseminated lupus) or one of cystic pattern (scleroderma especially).

Conclusions

Collagen diseases are characterized by alterations of the ground substance of connective tissue in which precipitation of the mucopolysaccharides is the basic histochemical alteration. The diseases in this group have traditionally been considered as afflictions of one or the other part of the body but it must be emphasized that they actually are a body-as-a whole disease. The basic change is similar in all but speed of the developing reaction, the anatomic site of maximum change and the relationship between various areas of the body involved allow for separation. The

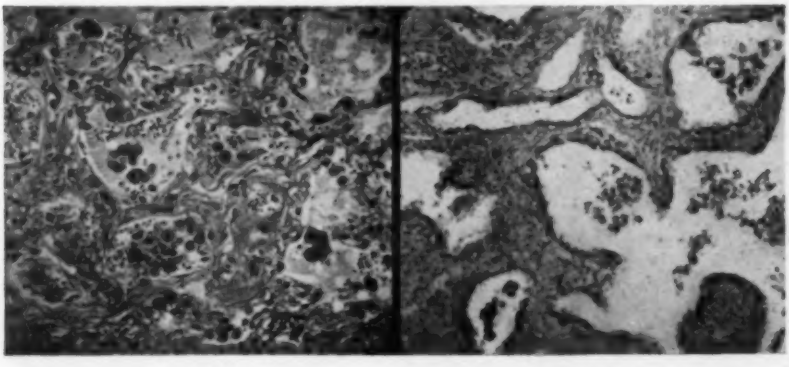


FIGURE 10 FIGURE 11

pulmonary changes of the collagen diseases affect the interstitial supporting tissues as well as the alveolar walls. The histo-anatomic alterations of alveolar septal fibrinoid necrosis, exudation, alveolar lining cell proliferation, organization, fibrosis, and cyst formation are described.

SUMMARY

Pulmonary alterations of the collagen diseases begin with the precipitation of the acid mucopolysaccharides in the alveolar wall, interstitial supporting tissue, blood vessels and lamina propria of the bronchioles. This basic change is accompanied by hemorrhage, exudation, fibrinoid necrosis, and proliferations of fibroblast and alveolar "lining" cells. This is followed by convalescence and repair, the speed of which varies with the nature of the disease. Eventually the involved areas show condensation of the collagen substance, rigidity of alveolar walls, vascular sclerosis and formation of irregular air cells in a cystic pattern. The changes develop most rapidly in acute rheumatic fever, lupus erythematosus and

FIGURE 12

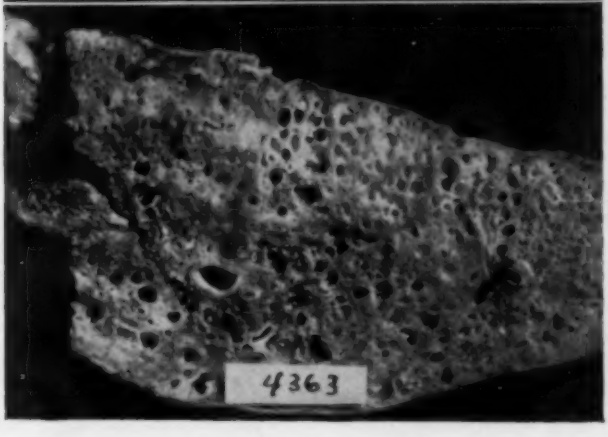


FIGURE 13

polyarteritis while in dermatomyositis and scleroderma the progress of change is more subtle and of longer duration. The pulmonary alterations are spotty, may be focal, but have exacerbations of remissions. There probably is no one cause which sets off the disease processes, but serious consideration points to an antigen-antibody reaction.

RESUMEN

Las alteraciones pulmonares en las enfermedades de la colágena empiezan por la precipitación de los mucopolisacáridos ácidos en la pared alveolar, en el tejido intersticial de soporte, en los vasos sanguíneos y en la lámina propia de los bronquiolos. Este cambio básico se acompaña de hemorragia, exudación, necrosis fibronoide, y proliferación de los fibroblastos y de las células alveolares de "recubrimiento." Esto es seguido por la convalescencia y reparación, la velocidad de la cual varía con la naturaleza de la enfermedad. A veces las áreas comprometidas muestran condensación de la substancia colágena, rigidez de las paredes alveolares, esclerosis vascular y formación de células de aire en forma de quistes. Este cambio se presenta más rápidamente en la fiebre reumática aguda, en el lupus eritematoso y en poliarteritis en tanto que en la dermatomiositis y en escleroderma la marcha del cambio es más sutil y de más larga duración. Las alteraciones pulmonares son localizadas, pueden ser focales pero tiene exacerbaciones y después de las remisiones. Probablemente no existe causa única para desencadenar la enfermedad pero una seria consideración señala hacia una reacción antígeno-anticuerpo.

RESUME

Les altérations pulmonaires dues aux maladies du collagène commencent par la précipitation des mucopolysaccharides acides dans la paroi alvéolaire, le tissu interstitiel de soutien, les vaisseaux sanguins et la membrane propre des bronchioles. Cette modification de base s'accompagne d'hémorragies, de secrétion, de nécrose fibreuse et de proliférations de fibroblastes et de cellules "bordantes" alvéolaires. Puis viennent la convalescence et la guérison; la rapidité de l'évolution varie avec la nature de l'affection. Eventuellement, les zones atteintes montrent des condensations de substance collagène, une rigidité des parois alvéolaires, de la sclérose vasculaire, et la formation de cellules aériques irrégulières, à type kystique. Les altérations se développent plus rapidement dans le rhumatisme articulaire aigu, le lupus érythémateux et la polyartérite, tandis que dans la dermatomyosite et la sclérodermie, le progrès des altérations est plus discret et de plus longue durée. Les lésions pulmonaires peuvent être localisées en foyer, et subissent des alternatives d'exacerbations et de rémissions. Il n'y a probablement pas une cause unique qui déclenche le processus de la maladie, mais une étude sérieuse de cette affection oriente vers une réaction antigène-anticorps.

ZUSAMMENFASSUNG

Pulmonale Veränderungen bei Bindegewebs-Erkrankungen beginnen mit der Ausfällung der sauren Mucopolysaccharide in der alveolarwand,

dem interstitiellen Stützgewebe, den Blutegefässen und der lamina propria der Bronchiolen. Die grundlegende Umwandlung ist verknüpft mit Haemorrhargie, Exsudation, fibrinoider Nekrose und Wucherungen der Fibroblasten und alveolären "Grenz-Zellen." Daran an schliesst sich Rekonvaleszenz und Wiederherstellung, deren Tempo je nach der Natur der Krankheit wechselt. Möglicherweise zeigen die betroffenen Gebiete Verdichtungen der kollagenen Substanz, Starre der Alveolarwände, Gefäss-Sklerose und Ausbildung unregelmässiger Luftzellen von cystischem Charakter. Die Veränderungen entwickeln sich am schnellsten bei akutem rheumatischen Fieber, lupus erythematosus und Polyartritis, während bei der Dermatomyositis und dem Skleroderm das Fortschreiten der Veränderung mehr schleichend erfolgt und von längerer Dauer ist. Die pulmonalen Umwandlungen sind schwach, können von fokalem Charakter sein, aber es kommen Exazerbationen vor nach vorübergehenden Remissionen. Wahrscheinlich besteht nicht nur eine Ursache, die die Krankheitsvorgänge in Gang setzt; mas muss jedoch ernsthaft eine Antigen-Antikörper-Reaktion in Erwägung ziehen.

REFERENCES

1 Klemperer, P.: "Diseases of the Collagen System," *Bull. New York Acad. Med.*, 23:581, 1947.

2 Klemperer, P.: "The Concept of Collagen Diseases," *Am. J. Path.*, 26:505, 1950.

3 Klemperer, P.: *Progress in Fundamental Medicine*, edited by J. F. A. McManus, 1952, London, p. 50.

4 Robb-Smith, A. H. T.: "The Concept of the Collagen Diseases," *Practitioner*, 173: 117, 1954.

5 Altshuler, C. H. and Angevine, D. M.: "Histochemical Studies on the Pathogenesis of Fibrinoid," *Am. J. Path.*, 25:1061, 1949.

6 Rich, A. R.: "The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy," *Bull. Johns Hopk. Hosp.*, 71:123, 1942.

7 Lustok, M. J. and Kuzma, J. F.: "Rheumatic Fever Pneumonitis: A Clinical and Pathological Study of 35 Cases," *Ann. Int. Med.*, 44:337, 1956.

8 Duthie, J. J. R.: "Rheumatism, Collagen and Cortisone," *Practitioner*, 173:125, 1954.

9 Miller, H.: "Polyarteritis Nodosa," *Practitioner*, 173:133, 1954.

10 Dowling, G. B.: "Lupus Erythematosus," *Practitioner*, 173:140, 1954.

11 Sommerville, J.: "Scleroderma and Dermatomyositis," *Practitioner*, 173:151, 1954.

12 Ellman, P. and Cudkowicz, L.: "Pulmonary Manifestations in the Diffuse Collagen Diseases," *Thorax*, 9:46, 1954.

13 Rubin, E. H.: "Pulmonary Lesions in 'Rheumatoid Disease' with Remarks on Diffuse Interstitial Pulmonary Fibrosis," *Am. J. Med.*, 19:569, 1955.

14 Edwards, J. E., Parkin, T. W. and Burchell, H. B.: "Recurrent Hemoptysis and Necrotizing Pulmonary Alveolitis in a Patient with Acute Glomerulonephritis and Periarteritis Nodosa," *Staff Meetings of the Mayo Clinic*, 29:193, 1954.

15 Spence, M. P.: "Rheumatoid Disease of the Lungs and Pleura," *Arch. Middlesex Hosp.*, 5:95, 1955.

16 Opie, L. H.: "The Pulmonary Manifestations of Generalized Scleroderma (Progressive Sclerosis)," *Dis. Chest*, 28:665, 1955.

17 Moersch, H. J., Purnell, D. C. and Good, C. A.: "Pulmonary Changes Occurring in Disseminated Lupus Erythematosus," *Dis. Chest*, 29:166, 1956.

The Rising Incidence of Isoniazid Resistance: Its Clinical Significance*

JACK REISS, M.D., F.C.C.P.** and SAM M. TOWNSEND, M.S.†
Coral Gables, Florida

With the advent of streptomycin in the treatment of pulmonary tuberculosis, it soon became evident that tubercle bacilli become resistant to the drug. This was particularly true in patients with cavitary disease. There was great concern among phthisiologists that the spread of streptomycin resistant tubercle bacilli might become a serious public health problem. Studies were soon begun, testing the drug susceptibility of tubercle bacilli recovered from patients.[1, 2, 3, 4, 5] When para-aminosalicylic acid (PAS) and isoniazid (INH) became available, it was soon noted that combinations of the drugs prolonged the period when the bacilli become resistant to streptomycin (SM).

At the Veterans Administration Hospital, Coral Gables, Florida, isoniazid sensitivity tests were performed on 322 consecutive patients of whom 133 had positive cultures from more than one specimen. Thirty-three (10 per cent) were resistant to 5 mcg. cc. of INH on the initial positive growth. None of the latter group had prior treatment with isoniazid as far as could be ascertained. Twenty-five had far-advanced and eight had moderately advanced disease.

An analysis of the 33 who were resistant to isonicotinic acid hydrazide at the start of therapy revealed that practically all with newly discovered disease with one exception (15 out of 16) became negative and arrested their disease in spite of initial resistance to isoniazid. These patients received combined drug treatment according to the Veterans Administration protocol. Ten received isoniazid (INH) plus streptomycin (SM) or isoniazid plus para-aminosalicylic acid (PAS), and six SM plus PAS.

The remainder of this group of 33 patients consisted of 17 with chronic cavitary disease, mostly of long duration (5 to 25 years). Only eight of this group became negative on chemotherapy, five were arrested, and three left against medical advice at a point when the sputa were negative. Nine remained problems of therapy. Patients with chronic cavitary disease may respond well to isoniazid for various intervals, in spite of initial resistance; however, the majority of them require a surgical procedure at the proper time to arrest their disease.

Experimentally the correlation between emergence of resistance to isoniazid and attenuation for guinea pigs is good.[6, 7] Might not the same process occur in human beings, giving the host an opportunity to counter-

From the Medical Service and Research Laboratories, Veterans Administration Hospital.

*Presented at Annual Conference, Florida Tuberculosis and Health Association, April 13-14, 1956.

**Chief, Pulmonary Disease Section, Medical Service.
†Bacteriologist.

act his infection? Two cases are presented to illustrate that primary resistance to INH *in vitro* does not necessarily indicate a poor clinical response.

Case Reports

Case 1: R. H., Sr., a 30 year old colored laborer, was admitted on Jan. 1, 1953, with history of productive cough for one year, fever, and loss of weight of thirty days duration. There is a history of chronic alcoholism and anti-luetic therapy in the service. He was acutely ill on admission and was started on 300 mg. of INH daily and SM gm. I, twice weekly. X-ray films on admission (Fig. 1) revealed evidence of disease, involving the entire right lung with a 2½ cm. cavity in the apex. There was also disease, involving the upper half of the left lung. Sputums were positive and original culture was resistant to all concentrations (5 mcg./cc. of INH). Sputum cultures one month and two months after start of therapy were resistant to all concentrations of INH and all concentrations of SM (100 mcg./cc.). Sputums became negative by smear and culture three months after start of therapy and remained negative until November 28, 1953, when he went AWOL. His final x-ray (Fig. 2) showed almost complete resolution of the pulmonary infiltrations and atelectasis of the right upper lobe.

This veteran was infected with tubercle bacilli which were initially resistant to INH and soon became resistant to SM in addition. His sputum converted and he showed an excellent clinical and radiological response. Follow up film three years later (Fig. 3) reveals atelectasis right upper lobe. He is working and has remained well.

Case 2: A. M., a 26 year old colored truck driver, was admitted to the hospital January 5, 1953, with a five month history of weakness, malaise, loose watery stools, cough, poor appetite and loss of 25 pounds. He was acutely ill. X-ray films revealed extensive bilateral pulmonary involvement with a large cyst in the upper lobe with honeycombing in the lower portion of the left upper lobe and exudative infiltration of upper two-thirds of the right lung (Fig. 4).

Sputums were positive for tuberculosis and initial culture revealed organisms resistant to all concentrations of INH. He was started on 100 mg. of INH t.i.d. daily and SM gm. I, twice weekly. After two months of therapy, the organisms were still resistant to INH and in addition to SM in all dilution (5 mcg./cc. INH and 100 mcg./cc. of SM). Sputum became negative by smear and culture four and a half months after institution of treatment and remained negative until discharge. Pneumoperitoneum was started February 12, 1953. X-ray film (Fig. 5) just prior to surgery revealed fluid level in large cyst in left upper lobe. On November 17, 1953, left upper lobectomy was performed, a thoracoplasty, and decortication of the left lower lobe. He had a stormy postoperative course but recovered. On February 15, 1954, he left the hospital AWOL. (Sputums were negative by smear and culture for seven months). X-ray film (Fig. 6), following left upper lobectomy and thoracoplasty.

His sputum converted and he showed considerable x-ray film and clinical improvement on the two drugs to which he was resistant; however, surgical intervention was required to bring him to an inactive status.

Discussion

Resistance to drugs *in vitro* does not necessarily indicate resistance *in vivo*. The period during which isoniazid remains effective in patients is still to be determined. On the basis of this small series of cases no definite conclusions can be drawn. However, there seems to be a rising incidence of primary resistance to isoniazid in patients on admission to this hospital. The Veterans Administration[8] has reported (20 hospitals reporting) an incidence of 9.3 per cent initial resistance to 1 and 5 mcg./cc. of INH. Meyer and Durand report an incidence of 8.03 per cent of primary resistance to 5 mcg. of INH.[9] The problem of possible attenuation of isoniazid-resistant tubercle bacilli for human beings is a complex one; however, this study indicates that isoniazid resistance may not have the fearful connotation connected with resistance to streptomycin and para-aminosalicylic acid.

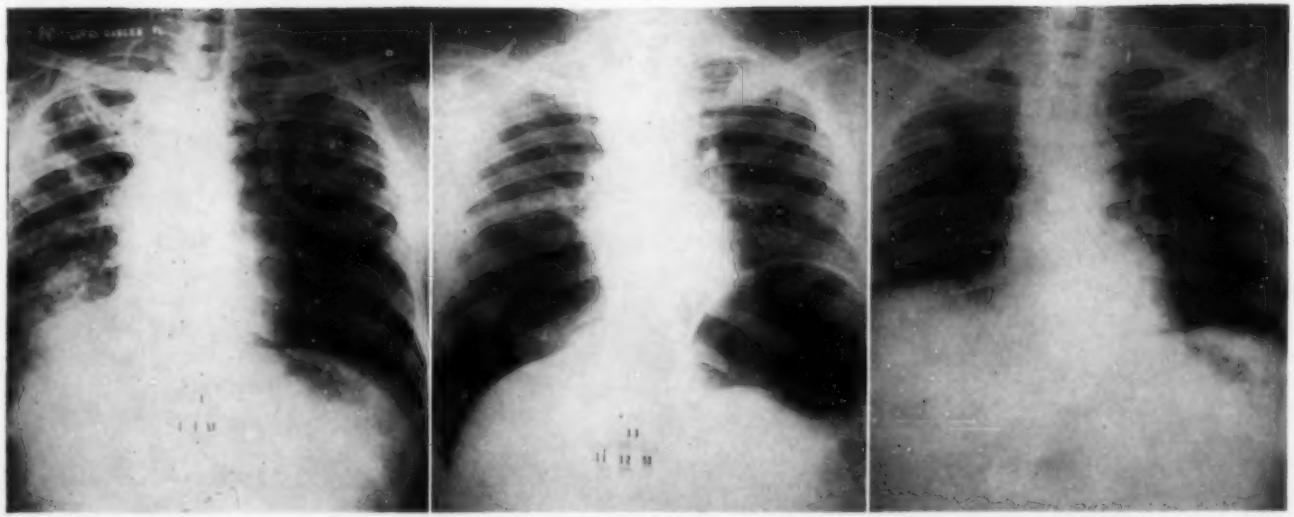


FIGURE 1 FIGURE 2 FIGURE 3

Figure 1 (Case 1): Admission x-ray film reveals exudative lesion, involving the entire right lung with a 2½ cm. cavity in the apex and an exudative lesion involving upper half of the left lung.—*Figure 2* (Case 1): X-ray film prior to discharge reveals complete resolution of the pulmonary infiltrations and atelectasis of the right upper lobe.—*Figure 3* (Case 1): Follow up film three years later reveals atelectasis of right upper lobe.

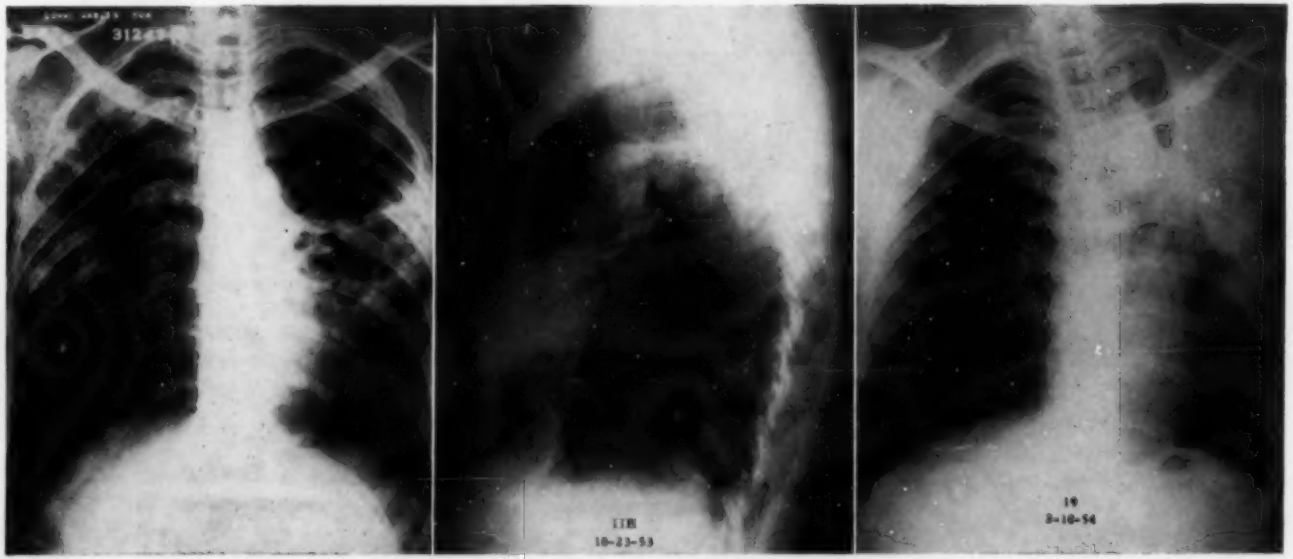


FIGURE 4 FIGURE 5 FIGURE 6

Figure 4 (Case 2): Admission x-ray film reveals extensive bilateral pulmonary involvement with a large cystic cavity in the left upper lobe, honeycombing in the lower portion of the left upper lobe and infiltration of upper two-thirds of the right lung.—*Figure 5* (Case 2): Left lateral x-ray film just prior to surgery shows fluid level in the large cystic cavity in the left upper lobe.—*Figure 6* (Case 2): X-ray film following left upper lobe lobectomy and thoracoplasty.

SUMMARY

1. In a series of 322 consecutive patients, an incidence of primary resistance to isoniazid of 10 per cent was demonstrated.

2. Newly diagnosed cases of pulmonary tuberculosis respond well to combined drug regime in spite of initial resistance to isoniazid.

3. Patients with chronic cavitary tuberculosis of long duration who are initially resistant to INH may respond well to combined chemotherapy; however, most of them require surgical help to effect an arrest of their disease.

4. Drug resistance has thus far not become a public health problem in newly discovered untreated patients.

RESUMEN

1. Se demostró la frecuencia de la resistencia primaria a la isoniacida en diez por ciento de 322 enfermos en serie consecutiva.

2. A pesar de la resistencia inicial a la isoniacida los nuevos casos de tuberculosis responden bien a los regímenes de drogas combinadas.

3. Los enfermos con tuberculosis cavitaria crónica de larga duración que inicialmente son resistentes a la isoniacida pueden responder bien a la drogoterapia combinada; sin embargo, la mayoría de ellos requieren de la cirugía para obtener la detención de su enfermedad.

4. La resistencia a las drogas hasta ahora, no se ha constituído en un problema de salubridad pública en los nuevos casos descubiertos sintratamiento.

RESUME

1. Sur un groupe de 322 malades, les auteurs ont pu déceler 10% de résistance à l'isoniazide avant tout traitement.

2. Les cas de tuberculose pulmonaire précocément diagnostiqués répondent bien au traitement par l'association médicamenteuse malgré le résistance initiale à l'isoniazide.

3. Les malades atteints depuis longtemps de tuberculose cavitaire, qui sont d'emblée résistants à l'isoniazide, peuvent répondre favorablement au traitement chimiothérapique combiné; toutefois la plupart d'entre eux ont besoin d'un complément chirurgical pour obtenir la stabilisation de leur affection.

4. La résistance à la chimiothérapie n'est pas devenue un problème sanitaire chez les malades découverts récemment, et qui n'ont pas encore été traités.

ZUSAMMENFASSUNG

1. In einer Reihe von 322 aufeinander folgenden Kranken wurde ein Vorkommen einer primären Resistenz gegen INH in 10% nachgewiesen.

2. Frisch erkannte Fälle von Lungentuberkulose reagieren günstig auf eine kombinierte medikamentöse Verordnung trotz initialer Resistenz gegen INH.

3. Kranke mit chronischer cavitäter langdauernder Tuberkulose, die anfänglich resistent gegen INH sind, können günstig auf kombinierte Chemo-

Therapie reagieren; die meisten von ihnen benötigen jedoch chirurgische Hilfe, damit es zu einem Stillstand ihrer Erkrankung kommt.

4. Arzneimittel-Resistenz hat sich somit nicht zu einem Problem der öffentlichen Gesundheitsfürsorge entwickelt in den Fällen von frisch entdeckten unbehandelten Patienten.

REFERENCES

1 Furtos, N. D. and Doane, E. A.: "Transmission of Streptomycin Resistant Tubercle Bacilli in Man," *J.A.M.A.*, 140:1274, 1949.

2 Brennan, A. J. and Wichelhausen, R. H.: "Streptomycin-Resistant Tubercle Bacilli," *J.A.M.A.*, 140:1275, 1949.

3 Thomas, O. F., Borthwick, W. M., Horne, N. W. and Crofton, J. W.: "Infection with Drug-Resistant Tubercle Bacilli," *Lancet*, 1:1308, 1954.

4 Cummings, M. M. and Livings, D. G.: "The Prevalence of Streptomycin-Resistant Tubercle Bacilli Among 5,526 Patients Admitted to Hospitals," *Am. Rev. Tuberc.*, 70:637, 1954.

5 Editorial: "Streptomycin-Resistant Tubercle Bacilli as a Public Health Hazard," *New England J. Med.*, 251:584, 1954.

6 Peizer, L. R., Minkin, A. and Wideloch, D.: "A Further Study of Virulence in Guinea Pigs of Isoniazid Resistant Tubercle Bacilli Isolated from Clinical Material," *Am. Rev. Tuberc.*, 70:728, 1954.

7 Conalty, M. L. and Gaffney, E. E.: "Studies on Izoniazid-Resistant Strains of Mycobacterium Tuberculosis," *Am. Rev. Tuberc.*, 71:799, 1955.

8 Dye, W. E.: Bacteriologist: Personal Communication, Oteen, N. C.

9 Meyer, L. and Durand, M.: "Rising Incidence of Isoniazid Resistance in Patients on Admission to the Sanatorium," *Rev. de la tuberc.*, 18:740, 1954. (Abstract in *Am. Rev. of Tuberc.*, 71:128, 1955.)

10 Oestreicher, R., Dressler, S. H., Russel, W. F., Jr., Grow, J. B. and Middlebrook, G.: *Observations on the Pathogenicity of Isoniazid Resistant Mutants of Tubercle Bacilli for Tuberculous Patients.* Trans. 14th Conf. Chem. of T. B., VA Army, Navy, 207, 1955.

The Significance of Cardiopulmonary Reserve in the Late Results of Pneumonectomy for Carcinoma of the Lung*

WILLIAM E. ADAMS, M.D., F.C.C.P., JOHN F. PERKINS, JR., M.D.,
ROBERT W. HARRISON, M.D., WALTER BUHLER, M.D.
and EDWIN T. LONG, M.D.

Chicago, Illinois

Inadequate explanation as to the cause of death following total pneumonectomy in older people has repeatedly confronted surgeons. Pulmonary insufficiency has been the most common diagnosis given to these fatalities without a clear understanding as to the basis for its development. That the reserve of pulmonary function is considerable in young, healthy individuals has been well appreciated for some time. This is substantiated by the fact that either total pneumonectomy or a bilateral resection of as much as 50 per cent of the lung is well tolerated following which a relatively normal active life may be enjoyed. Physiological studies in such individuals have shown little deviation in the normal blood picture (RBC and Hb.), blood chemistry (oxygen saturation), blood volume or pulmonary artery pressures. In young individuals (under 30 years of age) pulmonary capacity may be reduced in stages to as little as 40 per cent without great disturbance of cardio-pulmonary function during rest.

In 1931 it was demonstrated in these laboratories, that the pulmonary capacity in young, healthy dogs could be reduced to as little as one upper lung lobe or a functioning capacity of approximately 15 per cent.[1] This reduction in capacity was accomplished by completely stenosing the major bronchi in stages using a 35 per cent solution of silver nitrate applied through a bronchoscope. Following such a reduction in lung capacity, some compensatory elevation of elements in the blood were seen, which were only temporary in nature.

Total pneumonectomy became the operative procedure of choice in the treatment of carcinoma of the lung following Graham's successful case in 1933. Most patients tolerated the operation well, however in some fatalities occurring within three weeks after operation an adequate cause of death was frequently lacking. This stimulated further studies on dogs where it was found that although the blood picture and chemistry were little changed by the reduction of lung capacity to as little as 25 per cent of normal, alteration of hemodynamics could be of considerable significance.[2]

In a study of pulmonary hemodynamics in a group of 30 dogs, it was

*From the Departments of Surgery and Physiology of the University of Chicago.

This work was supported in part by United States Public Health Grant No. H-1894 (C6), in part by the E. F. Andrews Fund for Thoracic Surgery and in part by the Douglas Smith Foundation for Medical Research of the University of Chicago. We are indebted to Miss Joan Schick for valuable technical assistance.

Presented at the Fourth International Congress on Diseases of the Chest, American College of Chest Physicians, Cologne, Germany, August 19-23, 1956.

found that an elevation in pulmonary artery pressure could be expected after the removal of one lung. The average amount of elevation in this group of animals was from an original of 32/5 to 44/5 mm. of mercury following operation. This increase in pulmonary tension was maintained for at least several months. In a second group of 13 dogs where pulmonary resection was extended, in stages, to include the entire lung with the exception of one upper lobe or approximately 15 per cent of the total, the pulmonary tension increased from the original average of 32/5 to an average of 64/8 mm of mercury following surgery. Thus, the pulmonary artery pressure was increased by 100 per cent. Some of these animals died of spontaneous pneumothorax or of infection; however, most of them at autopsy demonstrated evidence of cardiac failure, a bloody, frothy material in the tracheobronchial tree and edema of the lungs being found. Four of the 13 animals survived this extensive pulmonary resection and appeared normal for several weeks or months following operation. Although an attempt was made to increase the survival rate by preventing overdistention of the remaining lung through the use of plastic sponge prosthesis in the pleural space following the initial operation, this procedure ended in complete failure.

In subsequent experiments, a study was made to determine the role of the vascular element (perfusion) versus the pulmonary element (diffusion) of the lung as a significant factor in the cause of death after pulmonary resection, and also to investigate the various factors which influence the development of pulmonary hypertension. Pulmonary artery pressures were obtained by means of a cardiac catheter. Increased demand for oxygen was produced by electrical stimulation of the muscles of the extremities. A total pneumonectomy was made in 10 healthy mongrel dogs weighing approximately 12 kg. six to 12 months prior to the studies being made. Before the experiment, a Number 8 French Catheter was introduced into a pulmonary artery via an external jugular vein. Heparin (0.5 mg/cu. cm. of saline) was used to maintain a patent catheter. Continuous recording of arterial blood oxygen saturation was made by means of an oximeter cuvette inserted between a carotid artery and an external jugular vein and connected to a recording oximeter which was designed by one of us (J. F. P.) and constructed in the physiology laboratory.[3] Heparin 5.0 mg/kg. intravenously, and 5.0 mg/kg. intramuscularly, was used to prevent clotting when the cuvette was connected. Just prior to obtaining the experimental data, an occlusion unit was placed around the pulmonary artery of the remaining lung, immediately below the branches to the left or right upper lobe. Thus, by occlusion of the vessel at this point it was possible to reduce the total pulmonary capacity from approximately 50 per cent to approximately 15 per cent of normal. In order to demonstrate more striking changes in pulmonary tension or arterial oxygen saturation when the pulmonary capacity was suddenly reduced to a maximum tolerance level, an apparatus for exercising the animal was connected to all four extremities. Exercise consisted of intermittent (60/min.) electrically stimulated contractions of the shoulder

girdle and the thigh muscles. A moderate to vigorous degree of exercise was used. The experiments were carried out with the dog breathing air or breathing 100 per cent oxygen. The results of these experiments were as follows: (1) pulmonary hypertension of serious import (up to 100 per cent increase of normal pressure) was produced in dogs by reducing lung capacity to 15-20 per cent of normal; (2) the accompanying fall in blood oxygen saturation was small (average 4.5 per cent) in view of the severity of the pulmonary hypertension; (3) when a demand for more oxygen was produced by exercise, a more severe grade of pulmonary hypertension was produced (as much as 200 per cent), as well as a much greater reduction in blood oxygen saturation; and (4) inhalation of 100 per cent oxygen restored the blood oxygen saturation to a normal level but did not alter the severity of the degree of pulmonary hypertension. Thus, the significance of pulmonary hypertension as a cause of death following pulmonary resection was demonstrated.[4]

Clinical studies dealing with this problem during recent years have substantiated the above findings observed in animal experimentation. Although pulmonary artery pressures in most patients under 50 years of age are little altered by total ablation of one lung, elevation following operation is not infrequently observed in older people. All too frequently, cardiac failure occurs from one to four or five weeks later due to markedly increased resistance to blood flow through the lungs. Our experience in this regard has been shared by others. The following two patients serve as illustrations.

Case 1: O. C., No. 58-08-62, a white man 66 years of age was prepared for removal of the right lung for primary carcinoma. He gave a history of productive

TABLE I

Blood O_2 Saturation and Pulmonary Artery Pressures in 6 Dogs Following Reduction of Pulmonary Capacity to 25–50%

Dog #	% Function	Duration	% Art. O_2 Saturation		% Ven. O_2 Saturation		Rt. Heart or PA Pressure	
			Rest	Exer.	Rest	Exer.	Rest	Exer.
936	25	7	100	97	65	53	32/6	59/0
925	25	6	97.5	95	-	-	33/0	57/1.6
901	25	7	95	88	62	57	41/6	75/9
872	25	6	96	98	68	62	42/13	57/14
17	25	7	93	85	-	-	50/2	80/0
895	50	6	97	94	-	-	37/0	54/0

cough and asthmatic symptoms of many years' duration. He was in good general condition with no evidence of weight loss. His blood pressure was 130/75 millimeters of mercury and the hemoglobin was 11.5 grams; he had no cardiac enlargement and the electrocardiographic findings were normal except for the influence of digitalis. Although blood oxygen saturation was lowered, there was only moderate reduction of pulmonary ventillatory function.

He withstood the operation satisfactorily. Mean pulmonary artery pressures before and following occlusion of that vessel were 39 and 53 cm. of water respectively, or an increase of 36 per cent following occlusion. Daily oximetric studies revealed a continuation of lowered blood oxygen saturation of 80 to 85 per cent, which was elevated to 95 per cent by the administration of only 4 liters of oxygen/minute via nasal oropharyngeal catheter.

He appeared to be progressing satisfactorily by the end of two weeks when he began to deteriorate. He died on the 26th post-operative day of cardiopulmonary failure.

Case 2: A. A., No. 59-28-60, a white man 60 years of age gave a history of productive cough for 15 years. Symptoms suggesting recent pulmonary pathology had been present for only two months. He appeared chronically ill and thin. His blood pressure was 120/80 millimeters of mercury and the hemoglobin 12.2 grams.; cardiac size was normal as were the electrocardiographic findings.

A total right pneumonectomy was necessary for removal of a primary carcinoma located near the hilum of the upper lobe. The mean pulmonary artery pressures before and following occlusion of the right pulmonary artery were 53 and 58 centimeters of water respectively. He responded satisfactorily during and following surgery and was discharged 14 days after operation. Because of his age and mild edema of the lower extremities he was put on digitalis. Six days following discharge he was readmitted because of signs of cardiac decompensation. Through an error he had taken no digitalis since leaving the hospital. An electrocardiogram showed evidence of a third degree heart block. There was progressive edema extending from the ankles to the thighs, dyspnea and orthopnea. The veins of the upper extremities were distended. The remaining left lung was clear. In spite of oxygen therapy and cardiac support, his condition deteriorated. Death due to right heart failure occurred one month following surgery.

Both of these patients were in the upper age group and gave a long history of productive cough due to a chronic pulmonary disorder. Both had mild pulmonary hypertension before surgery which was materially increased immediately following operation. Both tolerated surgery well but began to deteriorate two weeks later. In spite of the heroic use of all known therapeutic measures, both patients expired of excessive cardiac strain. In view of subsequent studies on dogs and patients, this outcome could have been predicted by the results of pulmonary hemodynamic studies. In one case there was no alternative to removal of the entire lung; in the other a lobectomy may have been sufficient. Thus, preoperative determination of the pulmonary artery or right heart pressure may be of great value in (1) diagnosis of preoperative right heart strain; (2) the decision as to how much lung may be safely removed; and (3) estimating prognosis following operation.

In 1955 Sloan, et al.[5] reported studies of a similar nature to those described above on patients, and arrived at similar conclusions. Pulmonary hypertension appeared to be associated with decreased cardiac output occurring during exertion. In 1956, at the annual meeting of the American Association of Thoracic Surgery, Hansen[6] in a discussion of several papers stated that in their experience a high percentage of the deaths following pneumonectomy was on the basis of cor-pulmonale. He recommended pulmonary artery occlusion prior to lung resection in order to determine if a shunt or hypertension was present. Thus, it appears beyond question that pulmonary hypertension of a significant degree may be anticipated following pneumonectomy in older people (over 60) and also in persons under 60 where lung tissue has been altered by emphysema or similar conditions. Furthermore, the degree of hypertension is usually markedly increased (75 to 100 per cent) by mild exercise. Knowledge of these facts argues in favor of less than a total pneumonectomy for carcinoma of the lung in older people where there appears to be a good chance of removing all tumor bearing tissue by such procedure.[3]

Arterial O_2 Saturation and Pulmonary Artery Pressures six to 12 Years Following Reduction of Pulmonary Capacity to 50 - 80 Per Cent in Dogs and Man. In view of the significance of pulmonary hypertension which accompanied reduction of pulmonary capacity in animals and man at the time of surgery, it was thought pertinent to repeat both pressure and O_2 saturation studies several years following operation. Compensatory changes within the lung with resultant diminution of pulmonary artery pressures as well as increasing degrees of obstructive hypertension were held as possibilities.

A. Animal experiments: This study is still in progress and a complete report will appear in a separate publication.[7]

Six dogs whose lung capacity had been reduced to 25 per cent of normal (50 per cent in one dog) six to seven years previously were subjected to this study. All determinations were made without narcosis (except novocaine locally) and while the animals were first at rest and then during exercise which consisted of running slowly on a treadmill at an 8 degree incline. Exercise was for periods of two and five minutes. Blood oxygen

TABLE II

Arterial O_2 Saturation and Pulmonary Artery Pressures in 8 Patients Following Reduction of Pulmonary Capacity to 50–80%

Patient	Age	% Function	Duration	% Art. O_2 Saturation		Rt. Heart or PA Pressure	
				Rest	Exer.	Rest	Exer.
P.C. 340966	68	50	12 yrs.	96.5	94.5	33/0	48/7
O.L. 378823	54	50	11 yrs.	90	86	56/0	85/0
S.D. 413797	65	50	9 yrs.	92	87	34/16	66/36
J.S. 592492	73	50	8 yrs.	96	90	75/35	112/45
M.H. 603120	69	80	2 yrs.	-	-	23/10	48/26
J.S. 451480	61	70	1-1/2 yrs.	92	82	32/0	53/2
H.T. * 146864	69	50	3-1/2 wks.	-	-	35/19	52/32**
O.C. * 580862	66	50	3 wks.	80	-	39/0	53/0**

* Expired

** Before and following pneumonectomy.

saturation values by oximeter couvette and pressures via cardiac catherization were obtained as in earlier experiments.

Results: As noted on Table I some pressures had returned to slightly above normal during the intervening years (from ^{50}-60/$_0$ to ^{32}-33/$_{0\text{-}6}$ mm. Hg.). Others had remained little altered. All pressures became more elevated on mild exercise, some by as much as 75 to 90 per cent. After resting for a period following five to 10 minutes of exercise, pulmonic and systemic pressures were at times lowered. This was interpreted as evidence of cardiac fatigue.

Blood oxygen saturation values were largely within normal limits while the animals were at rest, and were lowered only from 2 to 8 per cent during exercise. Thus, it would appear that relatively little adjustment had taken place following the reduction of lung capacity as related to the influence of exercise on an existing pulmonary hypertensive state.

In spite of these findings these dogs have continued to appear well nourished, and are active and normal in all other respects.

B. Human Studies Eight to 15 Years Following Pneumonectomy: These investigations are being made on 30 patients, only five of which have been completed at this time.[7]

The methods of study were similar to those described above for dogs, except that exercise was carried out in the supine position with the patient bicycling against resistance.

The results of these studies are seen in Table II. Data obtained at operation in two patients who expired of cor-pulmonale three to four weeks later are included in the Table for comparison, as are data on two cases obtained one and a half and two years following surgery.

Of the four late cases, two (O.L. and J.S.) are having considerable respiratory embarrassment, especially during mild exercise, and one (J.S.) has been in frank cardiac failure. The remaining two have continued to work full time at sedentary employment (desk work), but are short of breath on mild exertion. It will be noted that these latter two (P.S. and S.D.) had relatively normal pressures at rest, which became considerably elevated on mild exercise. A fifth patient, 15 years following surgery, revealed similar findings and was able to engage in only very light work.

Discussion

Reduction of lung capacity in dogs by pulmonary resection or bronchial occlusion (with resultant atelectasis) is not entirely comparable to reduction in patients by pneumonectomy. The remaining lung in dogs is perhaps more normal in its diffusion function ability, than is the lung tissue of older people who have some degree of emphysema or other degenerative changes. In spite of this, the reaction to this reduction in lung capacity was similar in man and dogs, both in the acute stage as well as several years following surgery. This was both true regarding diffusion function as well as pulmonary resistance with resultant hypertension. Both also reacted in a similar manner to the effect of exercise. The results of these studies would indicate that cor-pulmonale with ultimate cardiac failure is likely

responsible for a high percentage of fatalities which occur following pneumonectomy in patients with emphysema or other degenerative lesions.

Furthermore, as age increases following pneumonectomy, pulmonary reserve is apt to diminish. Thus, pulmonary hypertension may develop although there was little evidence of its presence at the time of surgery. This pressure will become further increased with exercise which demands greater cardiac output. Dyspnea on exertion will become manifested with advancing years.

Thus, in patients with peripheral lung lesions, resection of less than an entire lung should be strongly considered if there seems to be a reasonable chance of removing all tumor bearing tissue by this procedure.

SUMMARY

1. Pulmonary reserve in young people and dogs is very considerable. They may tolerate pneumonectomy without much resulting clinical handicap or physiologic change.

2. Pulmonary reserve in older individuals is decreased and in some cases a 50 per cent reduction in pulmonary capacity cannot be tolerated. Survival may be for three to five weeks, death being due to cardiac failure in spite of adequate blood oxygen saturation. Pulmonary artery pressure may be elevated as much as 25 to 50 per cent, and mild exercise increases cardiac strain by additional elevation of pulmonary artery pressures to as much as 75 to 100 per cent.

3. The ability of dogs to compensate for the ill-effects of reduced lung capacity to 20-25 per cent over a period of six to eight years following surgery is variable. All dogs develop pulmonary hypertension on mild exercise, to as much as twice the normal value in some instances.

4. Studies on five patients, eight to 15 years following pneumonectomy reveal varying degrees of pulmonary hypertension (from $^{33}/0$ to $^{75}/35$ mm. Hg.), following pneumonectomy which became additionally elevated on mild exercise to as much as 300 per cent of normal (from $^{48}/7$ to $^{112}/45$).

5. From these studies it seems reasonable to believe that pulmonary hypertension accounts for a high percentage of deaths following total pneumonectomy in older people. Furthermore, the resection of less than an entire lung should be seriously considered in carcinoma of the lung, if it appears possible to remove all tumor bearing tissue by that procedure.

RESUMEN

1. La reserva pulmonar en las personas jóvenes y en los perros es muy considerable. Pueden ellos tolerar la neumonectomía sin gran desventaja ni cambio fisiológico.

2. La reserva pulmonar en más personas de más edad disminuye y en algunos casos un 50 por ciento de reducción no puede tolerarse. La sobrevida puede llegar a tres a cinco semanas sobreviniendo la muerte por insuficiencia cardiaca a pesar de una adecuada oxigenación a saturación de

la sangre. Las presiones en la arteria pulmonar pueden elevarse hasta 25 a 50 por ciento y moderado ejercicio aumente el esfuerzo cardiaco por adicional aumento de la presión de la arteria pulmonar que llega hasta 75 a 100 por ciento.

3. La posibilidad para los perros de compensar los malos efectos de una reducción de la capacidad pulmonar a 20 o 25 por ciento hasta un período de seis a ocho años después de la cirugía, es variable. Todos los perros desarrollan hipertensión pulmonar desqués de moderado ejercicio hasta tanto como del doble de los valores normales en algunos casos.

4. Los estudios en cinco enfermos, ocho de ellos por 15 años desqués de neumonectomía revelaron grados diversos de hipertensión pulmonar (de 33/0 a 75/35 Hg.) después de neumonectomía la que se elevó más con el ejercicio moderado hasta tanto como el 300 por ciento de lo normal (de 48/7a 112/45).

5. Según estos estudios parece razonable creer que la hipertensión pulmonar es la responsable de alto porcentaje de muertes después de la neumonectomía total en las personas de edad. Adenmás, la resección de menos de un pulmón completo debe ser considerada seriamente si parece posible el poder resecar todos los tejidos que compromete este tumor.

RESUME

1. Les réserves pulmonaires chez les gens jeunes et chez les chiens sont très grandes. Ils peuvent supporter une pneumonectomie sans trouble clinique considérable consécutif, et sans modification physiologique.

2. Les réserves pulmonaires sont diminuées chez les individus plus âgés et dans certains cas, ils ne peuvent supporter une réduction de 50% de la capacité pulmonaire. La survie peut atteindre 3 à 5 semaines, la mort étant due à un arrêt cardiaque, malgré une bonne saturation oxygénée sanguine. Les pressions de l'artère pulmonaire peuvent s'élever de 25 à 50% et un faible effort augmente la fatigue du coeur de 75 à 100%.

3. Pour les chiens la possibilité de compenser de 20 à 25% la réduction de la capacité pulmonaire est variable, et s'étend sur un délai de 6 à 8 ans après l'intervention. Tous ces chiens présentent une hypertension pulmonaire après un faible exercice. Elle peut atteindre dans ces cas jusqu'à deux fois la valeur normale.

4. Des études poursuivies sur cinq malades suivis pendant un délai de 8 à 15 ans après pneumonectomie, montrent différents degrés d'hypertension pulmonaire. Cette hypertension peut s'élever encore davantage après un faible effort, et atteindre alors 300% du taux normal.

5. D'après ces études, il semble rationnel d'admettre que l'hypertension pulmonaire entre pour une proportion élevée dans les causes de morts consécutives à une pneumonectomie totale chez les malades âgés. C'est pourquoi la résection partielle d'un poumon doit être envisagée dans le cas de cancer pulmonaire, s'il semble possible d'enlever ainsi toute la portion de tissu envahi par le processus tumoral.

ZUSAMMENFASSUNG

1. Die pulmonale Reserve bei jungen Menschen und Hunden ist sehr beträchtlich. Die können eine Pneumonektomie vertragen ohne viel nachfolgendes Handicap oder physiologische Veränderungen.

2. Die pulmonale Reserve bei älteren Individuen ist herabgesetzt, und in manchen Fällen kann eine Verminderung der Lungenkapazität von 50% nicht vertragen werden. Die Überlebenszeit kann 3-5 Wochen betragen und der Tod ist die Folge eines cardialen Versagens trotz adäquater Sauerstoffsättigung des Blutes. Die pulmonalen Arteriendruckwerte können bis 25 und 50% erhöht sein, und leichte Anstrengung verstärkt die cardiale Überlastung durch zusätzliche Erhöhung der pulmonalen arteriellen Druckwerte bis zu einer Höhe von 75 bis 100%.

3. Die Fähigkeit von Hunden, die Nebenwirkungen der verringerten Lungenkapazität auf 20 bis 25% für einen Zeitraum von 6-8 Jahren anschliessend an die Operation zu kompensieren, ist verschieden. Bei allen Hunden entwickelt sich ein pulmonaler Hochdruck bei leichter Anstrengung bis zum Doppelten des normalen Wertes in manchen Fällen.

4. Untersuchungen an 5 Kranken 8-15 Jahre nach der Pneumonektomie ergaben variirende Grade von pulmonalem Hochdruck (von 33:0-75:35 mm. Hg.) nach der Pneumonektomie, der eine zusätzliche Erhöhung erfuhr bei leichter Belastung, und zwar bis zu 300% des Normalen (von 48.7-112:45).

5. Anhand dieser Untersuchungen scheint die Annahme nase zu liegen, dass der pulmonale Hochdruck verantwortlich ist für einen hohen Prozentsatz an Totesfällen anschliessend an eine totale Pneumonektomie bei älteren Personen. Darüber hinaus muss dann die Resektion von weniger als einer ganzen Lunge ernsthaft in Erwägung gezogen werden beim Lungencarcinom, wenn es möglich erscheint, durch ein solches Vorgehen das gesamte geschwulsthaltige Gewebe zu entfernen.

REFERENCES

1 Adams, W. E.: "Subtotal Atelectasis and Pneumonectomy in Dogs," *Proc. Soc. Exp. Biol. and Med.*, 28:957, 1931.

2 Carlson, R. F., Charbon, B. C., Charbon, H. G. H. and Adams, W. E.: "The Effect of Decreasing the Amount of Lung Tissue on the Right Ventricular Pressures in Animals," *J. Thoracic Surg.*, 21:621, 1951.

3 Perkins, J. F. Jr., Adams, W. E. and Livingstone, H.: "The Conversion of Millikan and Wood Type Oximeter into Direct-writing Recording Instruments for Use in Surgery, in Studies of Pulmonary Function and in Teaching Respiratory Physiology," *J. Lab. and Clin. Med.*, 40:457, 1952.

4 Adams, W. E., Perkins, J. F. Jr., Flores, A., Chao, P. and Costellanos, M.: "The Significance of Pulmonary Hypertension as a Cause of Death Following Pulmonary Resection," *J. Thoracic Surg.*, 26:407, 1953.

5 Sloan, H., Morris, J. D., Figley, M. and Lee, R.: "Temporary Unilateral Occlusion of the Pulmonary Artery in the Pre-operative Evaluation of Thoracic Patients," *J. Thoracic Surg.*, 30:591, 1955.

6 Hansen, H.: (Stockholm, Sweden). *Discussion—Meeting of American Association Thoracic Surgery*, Miami Beach, May 1956.

7 Harrison, R. W., Adams, W. E., Long, E. T. and Buhler, W.: "Comparison of the Effects of Acute and Chronic Reduction of Lung Volumes on Cardiopulmonary Reserve," *AMA Archives of Surgery.* In press.

An Evaluation of Digitalis Tolerance with Acetyl Strophanthidin

LEE EHRLICH, M.D., F.C.C.P., BERNARD M. LIPSCHULTZ, M.D.
and JOE C. EHRLICH, M.D., F.C.C.P.

Phoenix, Arizona

The determination of the state of digitalization in a given patient is often difficult and at times impossible. Although Eggleston[1] indicated that the required quantity of digitalis is a function of body weight, the digitalizing dose is an empiric and occasionally a dangerous assumption. Clinically, the classical symptoms of digitalis intoxication may mimic those of circulatory failure. Nausea, vomiting, and abdominal distress may be secondary to hepatic and visceral congestion; premature ventricular systoles may be a manifestation of myocardial anoxia; and paroxysmal tachycardia may indicate excessive or inadequate digitalis administration. The electrocardiogram indicates digitalis effect, but no quantitative correlation with the S-T segment and T wave changes exists. Only with the electrocardiographic appearance of auriculoventricular block, premature ventricular systoles, bigeminus rhythm, nodal rhythm, etc., is toxicity apparent.

It, therefore, becomes evident that the need for a test designed to establish proper digitalization exists. In an attempt to fulfill this need, Lown and Levine[2] recently described the acetyl strophanthidin test, employing the synthetic ester of the cardiac aglycone, strophanthidin, obtained from the seeds of Strophanthus kombe (Fig. 1).

That acetyl strophanthidin possesses a digitalis-like action has been extensively proved. Chen and Elderfield[3] produced systolic standstill of the frog ventricle and emesis in cats following sublethal doses administered intravenously. Greiner and Reilly[4] demonstrated myocardial contraction as judged on an isolated hypodynamic papillary muscle. Gold et al[5] found that acetyl strophanthidin produced essentially the same kind of effects as the digitalis glycosides in man, such as slowing of the ventricular rate in atrial fibrillation, nausea, vomiting, and alleviation of the symptoms of cardiac failure. That it potentiates ouabain in the production of ventricular tachycardias has been well shown by Enselberg et al.[6]

The attempt to determine the state of digitalization by the employment of an additional intravenous glycoside is not new. In 1943, LaDue and Fahr[7] employed lanatoside C, but the delayed action of this drug militates against its practical value. Griffith[8] employs 0.5 mgm. of ouabain diluted to 20 cc., injecting at the rate of 1 cc. per minute. When the cardiac rate slows perceptively, he feels he is getting good digitalis effect; if an arrhythmia or tachycardia ensues, toxic effects are presumed to have occurred and the ouabain test dose is discontinued.

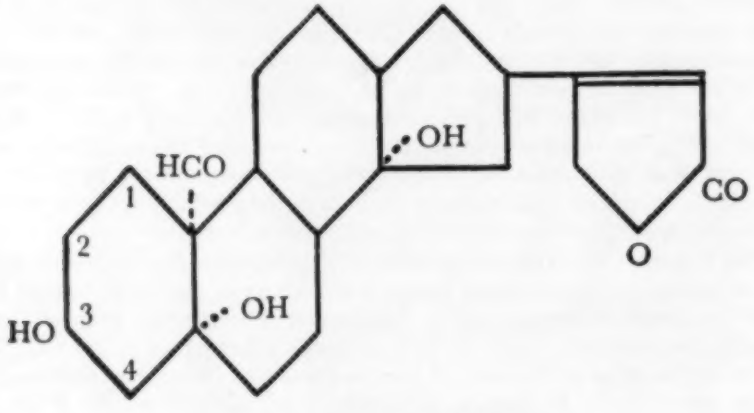
From the Medical Service, Veterans Administration Hospital.

The advantage of a preparation possessing a short latent period of action and rapid dissipation becomes evident by comparison of acetyl strophanthidin with ouabain (Table I). Acetyl strophanthidin exerts its earliest effect within ½ to five minutes, reaches its peak action at 12 minutes, and is dissipated completely in two hours. The effect of ouabain is clinically first noted at five to 20 minutes, reaches its peak at one to two hours, and is completely eliminated from three hours to five days. The advantages of acetyl strophanthidin, therefore, are its short latent period, short dissipation, and short period of potential toxicity.

Technique of Acetyl Strophanthidin Digitalis Tolerance Test

Two cc. of acetyl strophanthidin (6 cat units or 1.1 mgm.) is diluted to 20 cc. with 5 per cent glucose in water. If the patient has received small amounts or no digitalis, 5 cc. is injected intravenously every five minutes until the desired therapeutic effect or toxic effect electrocardiographically appears. For those patients who have been digitalized, the dosage interval may be lengthened to 10 minutes, although in our cases a five-minute dosage interval proved satisfactory. These effects are followed by means of a continuous direct-writing electrocardiograph.

According to Lown and Levine's[2] experience with 20 tolerance tests, if toxicity developed after the first injection of 0.27 mgm. of acetyl strophanthidin, over-dosage was present. If toxicity ensued after 0.55 mgm. the patient was considered to be adequately digitalized. When therapeutic action occurred after 0.82 mgm., fractional doses of digitalis were indicated, and if 1.1 mgm. or more was required, full digitalization was necessary. Evidence of acetyl strophanthidin over dosage consisted of the appearance of ventricular premature systoles, acceleration of the auricular rate, changes in the contour of the P wave, and prolonged auriculo-ven-



Strophanthidin

FIGURE 1: From *Current Concepts in Digitalis Therapy*. Lown, B. and Levine, S. A.: Little, Brown & Co., Boston, 1954.

TABLE I

COMPARISON OF SPEED OF ACTION AND DISSIPATION OF OUABAIN AND ACETYL STROPHANTHIDIN*

Drug	Earliest Effect	Peak Action	Persistence of Effect	Duration of Toxicity
Ouabain	5 - 20 min.	60 - 120 min.	3 hr. - 5 days	Several hr.
Acetyl strophanthidin	½ - 5	12	2 hr.	30 min.

*Note that action of acetyl strophanthidin is more rapid and more transient than that of ouabain.

From *Current Concepts in Digitalis Therapy.* Lown, B. and Levine, S. A.: Little, Brown & Co., Boston, 1954.

tricular conduction. In the presence of atrial fibrillation, the acceleration and regularization of the ventricular response indicating atrial tachycardia with block was considered significant.

Our plan was to evaluate the degree of digitalization and proximity to toxicity in patients receiving different preparations. Consequently, for this test a group of 10 patients presenting various etiologic forms of heart disease were selected. They were digitalized and maintained on either whole-leaf digitalis or digoxin. All had apparently been well digitalized as evidenced by slowing of the ventricular rate, objective and subjective subsidence of symptoms of congestive heart failure, along with the main-

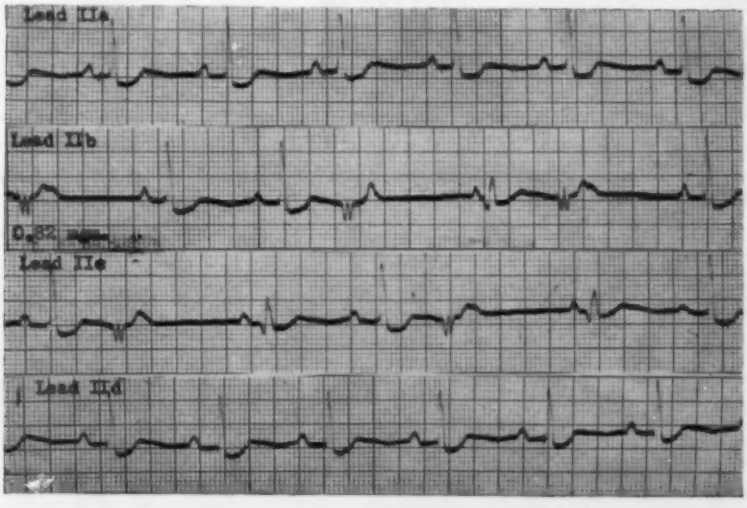


FIGURE 2: Patient R. G. N., age 65, arteriosclerotic heart disease on digoxin 0.50 mgm. All leads are lead II. IIa—No change immediately after 0.82 mgm. acetyl strophanthidin. IIb and IIc—Note development 2 minutes later of premature ventricular systoles of multi-focal origin. IId—Abolishment of premature ventricular systoles with 10 mgm. pronestyl intravenously.

tenance of a so-called "dry weight" for a minimum period of two weeks. In all instances, electrocardiographic evidence of digitalis effect upon the S-T segment and T wave was evident as compared to the initial pre-digitalization electrocardiogram.

Results of Test. Ten patients were tested by the aforegoing method: four patients with chronic cor pulmonale, four with arteriosclerotic heart disease, and two with hypertensive cardiovascular disease.

In this group of 10 apparently well-digitalized patients, electrocardiographic evidence of toxicity was achieved in only two. In one (Fig. 2) after 0.82 mgm. of acetyl strophanthidin, frequent multi-focal premature ventricular systoles were noted. This occurred in a 65-year-old white man with arteriosclerotic heart disease and indicated that he had incomplete digitalization and would require small further fractional doses of digitalis. The arrhythmia ceased after 100 mgm. of procaine-amide was administered intravenously.

In the second case (Fig. 3), a 41-year-old white man with chronic cor pulmonale, a transient nodal rhythm developed after 0.82 mgm. of acetyl strophanthidin. Again this test indicated incomplete digitalization.

In six cases, no change in the electrocardiographic pattern was noted with the administration of 1.1 mgm. of acetyl strophanthidin. In two cases, even 1.65 mgm. failed to produce electrocardiographic toxicity.

Conclusion

In our experience, the acetyl strophanthidin tolerance test possesses value in clinical cardiology only as an indicator as to whether or not more digitalis can be tolerated safely. This data may be of paramount significance in patients where digitalis has been taken erratically, where a supraventricular tachycardia or frequent premature systoles exist. That a significant and variable margin exists between the therapeutic and toxic doses is evident and has been emphasized previously. LaDue[7] was able to administer 1.6 mgm. of lanatoside C to fully digitalized patients. In our experience, full digitalizing doses of acetyl strophanthidin in similar patients elicited toxicity in only two of 10 cases. Lown[9] refers to this

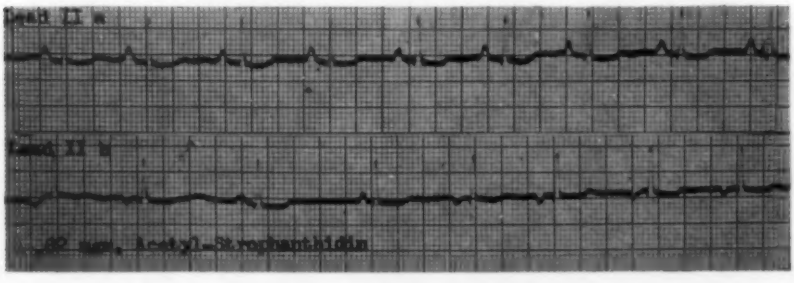


FIGURE 3: Patient H. S., age 41, with chronic cor pulmonale on 0.5 mgm. digoxin (Lead IIa). Lead IIb—Note development of nodal rhythm after 0.82 mgm. acetyl strophanthidin.

safety margin as the "insensitive area in the dosage response curve of drug action." In this relatively small number of cases, there were no apparent differences in the approach to toxicity with whole-leaf digitalis or digoxin. Lown and Levine's[2] data which indicate that groups of patients could be segregated on the basis of no digitalis, partial, complete, or excessive digitalization could not be confirmed. Moreover, it is unlikely in view of the wide and variable range between minimal adequate digitalization and toxicity in the individual patient that such a degree of accuracy could be obtained with any preparation.

Acknowledgments: The authors wish to express their appreciation to Eli Lilly and Company for their generous supply of acetyl strophanthidin.

SUMMARY

1. Experiences in ten digitalized patients utilizing acetyl strophanthidin as a digitalis tolerance test are related.

2. In eight of the ten cases, toxicity could not be elicited with full digitalizing doses of acetyl strophanthidin in previously adequately digitalized patients. This was true whether whole-leaf digitalis or digoxin was employed.

3. The acetyl strophanthidin test will indicate whether additional digitalis may be safely administered. It does not indicate the state or adequacy of prior digitalization. One cannot determine by this method, therefore, whether the patient has received any digitalis or is partially or completely digitalized.

RESUMEN

1. Se relatan las experiencias en diez enfermos digitalizados usando acetil-estrofantidina como prueba de tolerancia a la digital.

2. En ocho de los diez casos no se pudo provocar la toxicidada con dosis completas digitalizantes de acetil-estrofantidina en enfermos previamente y adecuadamente digitalizados. Ocurrió esto tanto cuando se usó hoja completa de digital como cuando se usó digoxina.

3. La prueba de la acetil-estrofantidina indicará cuando pue de proporcionarse más digital con seguridad. No indica el estado de la digitalización previa ni si éstá es adecuada. Por tanto, no se puede saber por este método si el paciente ha recibido digital o esparcial o completamente digitalizado.

RESUME

1. Les auteurs rapportent une expérience d'utilisation de l'acetyl-strophantidine comme test de tolérance chez 10 malades traités par la digitaline.

2. Dans huit de ces 10 cas, la toxicité ne put être mise en évidence avec des doses d'acetyl-strophantidine susceptibles de réaliser une digitalisation complète chez des malades antérieurement traités par la digitaline. Ceci fut vrai quelle que soit la préparation de digitaline utilisée.

3. Le test à la strophantidine permet de savoir si une dose supplémentaire de digitaline peut être administrée sans risque ou non. Il n'indique

pas l'état de "digitalinisation" antérieur. C'est pourquoi on ne peut déterminer par cette méthode si le malade a reçu antérieurement une certaine dose de digitaline, ou bien s'il subit partiellement ou de façon complète l'action de ce produit.

ZUSAMMENFASSUNG

1. Es werden Erfahrungen mitgeteilt an 10 digitalisierten Kranken unter Verwendung von Acetyl-Strophanthidin als Digitalis-Toleranz-Test.

2. Bei 8 der 10 Fälle konnte die Toxizität mit voll digitalisierenden Dosen von Acetyl-Strophanthidin bei zuvor entsprechend digitalisierten Kranken nicht festgestellt werden. Dies war der Fall, gleichgültig, ob Digitalis-Vollextrakte oder Digoxin benutzt wurde.

3. Der Acetyl-Stophanthidin-Test ergibt, ob noch zusätzlich Digitalis ohne Schädigung veordnet werden kann. Er zeigt aber nicht das Ausmass oder die Zulänglichkeit vorheriger Digitalisierung an. Man kaan daher mittels dieser Methode nicht feststellen, ob der Kranke überhaupt Digitalis erhalten hat oder teilweise oder vollständig digitalisiert ist.

REFERENCES

1 Eggleston, C.: "Digitalis Dosage," *Arch. Int. Med.*, 16:1, 1915.

2 Lown, B. and Levine, S. A.: "Current Concepts in Digitalis Therapy." Little, Brown & Co., Boston, 1954.

3 Chen, K. K. and Elderfield, R. C.: "Synthetic Derivatives of Strophanthidin," *J. Pharmacol. and Exper. Therap.*, 76:81, 1942.

4 Greiner, T. and Reilly, J.: "Inotropic Action of Acetyl Strophanthidin, Strophanthidin and Tryptamine-Strophanthidin," *Proc. Soc. Exper. Biol. and Med.*, 81:141, 1952.

5 Gold, H., Otto, H. L., Modell, E. and Halpern, S. L.: "Behavior of Synethetic Esters of Strophanthidin, the Acetate, Propionate, Butyrate, and Benzoate, in Man," *J. Pharmacol, and Exper. Therap.*, 86:301, 1946.

6 Enselberg, C. D., Altchek, M. R. and Hellman, E.: "The Action of Acetyl Strophanthidin in Rapid Cardiac Arrhythmias," *Am. Heart J.*, 40:919, 1950.

7 LaDue, J. S. and Fahr, G.: "Effect of Intravenous Administration of Lanatoside C Upon Output, Diastolic Volume, and Mechanical Efficiency of Failing Human Heart," *Am. Heart J.*, 25:344, 1943.

8 Griffith, G. C.: Personal communication from George C. Griffith, University of Southern California School of Medicine.

9 Lown, B.: Personal communication from Bernard Lown, Department of Medicine, Harvard Medical School.

Evaluation of Pharmacologic Tests as an Aid in Diagnosis of Pheochromocytoma: With Report of a Case of Pheochromocytoma and Tuberculosis*

GRACE M. ROTH, PH.D.** and WALTER F. KVALE, M.D.†
Rochester, Minnesota

Although intrathoracic pheochromocytomas are rare, as we reported previously,[1] the chest physician and chest surgeon should be aware of the hazards of such tumors and of the desirability of correct diagnosis before operation. When a patient with either paroxysmal or sustained hypertension has a tumor located paravertebrally in the thorax, the safe pharmacologic tests for pheochromocytomas may be employed. The information which they give may prevent the finding of an unexpected pheochromocytoma with an associated untoward reaction or even a fatality.

Of interest to the chest physician also is the occasional case in which a pheochromocytoma is associated with pulmonary tuberculosis and retards the response of the patient to treatment. The diagnosis of pheochromocytoma then may be highly important for the patient with tuberculosis.

Pheochromocytoma or the adrenal medullary tumor may be associated with sustained hypertension or with paroxysmal hypertension and attacks similar to those following the administration of large amounts of epinephrine or norepinephrine.

Occasionally a physician may be fortunate enough to observe a patient with paroxysmal hypertension in a spontaneous attack from pheochromocytoma, but he is more likely to have only the history of the attacks available. For the patient with sustained hypertension the physician may not have even a history of attacks to point the way to a correct diagnosis. Thus the pharmacologic tests may be helpful in screening relatively large numbers of patients for pheochromocytoma and can be of definite aid to a correct diagnosis.

The Pharmacologic Tests for Pheochromocytoma

As the first step in the pharmacologic tests we observe each patient for at least half an hour to obtain the correct basal blood pressure. This is highly important in the interpretation of the results after the use of histamine or regitine. When the patient has paroxysmal hypertension and a basal blood pressure of less than 170 mm. of mercury systolic and less

*Read at the Fifth International Congress on Diseases of the Chest, American College of Chest Physicians, Cologne, Germany, August 19 to 23, 1956.

**Section of Physiology, Mayo Clinic and Mayo Foundation.

†Section of Medicine, Mayo Clinic and Mayo Foundation.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

than 110 mm. diastolic, histamine[2] is used for the test. In our hands it is the most effective drug which we have found for use in tests for pheochromocytoma, for it stimulates the discharge of the pressor substances from the tumor and produces attacks similar to those that occur spontaneously. When the patient has mild hypertension and gives a history of paroxysmal attacks even though the basal blood pressure is less than 170/110 mm., both histamine and phentolamine methanesulfonate (regitine) may be used because regitine will lower the blood pressure if pressor substances released by pheochromocytoma are present in the blood. When the patient has sustained hypertension and a basal blood pressure of more than 170 mm. systolic and 110 diastolic, regitine [3, 4] and not histamine is administered because regitine will lower the blood pressure if a pheochromo-

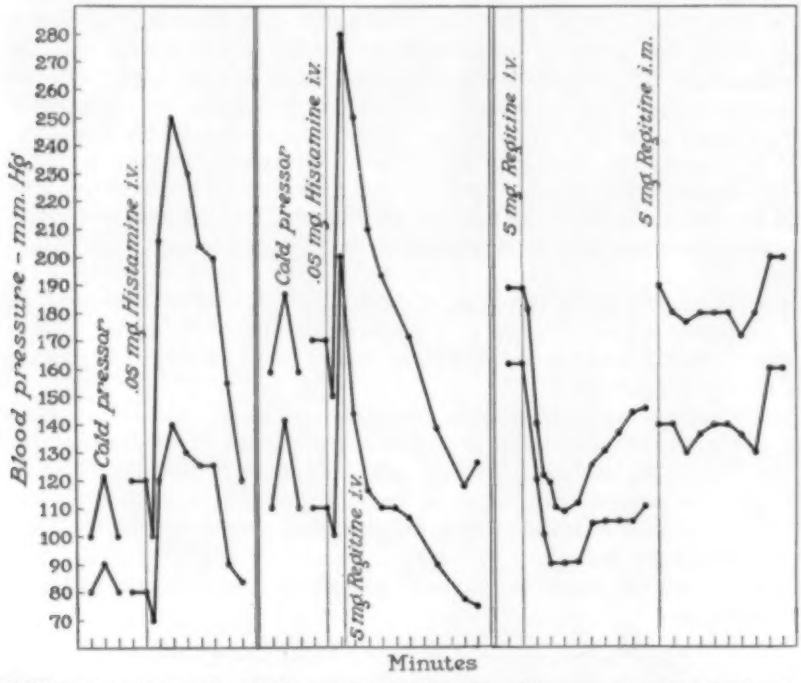


FIGURE 1: Changes in blood pressure during the cold pressor test, histamine test and regitine test. *Left:* The rise in blood pressure during immersion of one hand in cold water at 4° C. for 1 minute and after the intravenous administration of 0.05 mg. of histamine base in 0.5 cc. of physiologic solution of sodium chloride. Thirty seconds after the injection of histamine the blood pressure fell and 2 minutes later rose precipitously. This response indicates a pheochromocytoma. *Center:* The rise in blood pressure during the cold pressor test and the more precipitous rise following injection of histamine should be noted. At the height of the response to histamine, regitine, given intravenously, produced a precipitous fall in blood pressure together with a cessation of all clinical signs and symptoms. Thus two tests were positive for pheochromocytoma. *Right:* The sudden rapid fall of the blood pressure after the intravenous injection of 5 mg. of regitine is interpreted as a positive indication of pheochromocytoma. Practically no fall but instead a rise in the blood pressure followed intramuscular administration of 5 mg. of regitine. This indicates that a pheochromocytoma is not present. This was a false negative result in this case.

cytoma is present.

Before administration of either histamine or regitine, however, the cold pressor test is performed. This test is highly important in the interpretation of the results after the use of histamine.

The cold pressor test [5] is carried out by immersing one of the patient's hands to well above the wrist in water at 4° C., keeping it immersed for 1 minute, and measuring the blood pressure on the opposite arm 15, 30 and 60 seconds while the hand is placed in the water. The highest blood pressure after this painful stimulus represents the lability of the blood pressure. The cold pressor test is an integral part of the histamine test as the response of the blood pressure to cold is used for interpreting the response of the blood pressure 2 minutes after intravenous injection of histamine. When the blood pressure has returned to basal levels after the cold pressor test, the histamine test or regitine test may be started.

For the histamine test, as we carry it out, histamine is never given as an intravenous infusion but 0.05 mg. of histamine base in 0.5 cc. of normal saline solution is placed in a tuberculin syringe and is injected intravenously (Figure 1, *left*). The blood pressure is measured repeatedly for 10 minutes. The blood pressure always falls 30 seconds after the injection or the histamine did not enter the vein. Immediately thereafter the blood pressure rises rapidly and usually reaches the maximum in 2 minutes. If a pheochromocytoma is present, the characteristic clinical signs and symptoms of a severe episode appear concomitantly. In any one patient, one or more of the characteristic symptoms may be lacking.

The average increase in blood pressures of 21 patients with pheochromocytoma and normal blood pressures between attacks to histamine was 104 mm. of mercury systolic and 56 mm. diastolic. This was 60/20 mm. more than the average increase of the blood pressure during the cold pressor test.

For the patient with mild labile hypertension and a history of paroxysmal attacks, even though the basal blood pressure is less than 170/110, both histamine and regitine are used (Figure 1, *center*) as follows: the needle is left in the vein following the administration of histamine and another syringe containing regitine is attached. Repeated blood pressure readings are made for two minutes after the injection of histamine, then 5 mg. of regitine is injected. If the rise in blood pressure after the injection of histamine is due to the pressor amines from a pheochromocytoma, all symptoms will disappear and the blood pressure will fall in 30 to 60 secons after injection of regitine. Therefore, histamine may be given with safety and both tests will give positive results. If the patient has mild essential hypertension, the blood pressure will not rise as high after injection of histamine, and the headache will not disappear, nor will the blood pressure fall rapidly after injection of regitine. If regitine is given alone to the patient with labile hypertension between paroxysms, the blood pressure may rise in the presence of a tumor because there will be no pressor amine in the blood between attacks. Therefore a false negative result will be obtained.

For the patient with sustained hypertension,[4, 6] 5 mg. of regitine is administered intravenously, not intramuscularly. The blood pressure should fall at least 35 mm. of mercury systolic and 25 mm. diastolic for a positive result. The average fall in 18 patients with sustained hypertension was 78 mm. systolic and 46 mm. diastolic (Figure 1, *right*). The result of the test may be negative even in the presence of a tumor when regitine is given intramuscularly (Figure 1, *right*). It is true that regitine has a tendency to produce a fall in the blood pressure during the first minute after injection when no pheochromocytoma is present, but the blood pressure then returns to a level which will be considered negative for pheochromocytoma. False positive results generally occur for specific reasons.

If no previous medication has been administered, the histamine test yields a clear-cut positive or negative for the patient with paroxysmal hypertension and the regitine test gives an unequivocal result for the patient with sustained hypertension. Furthermore, these results may be obtained within an hour's time and the tests may be carried out by the

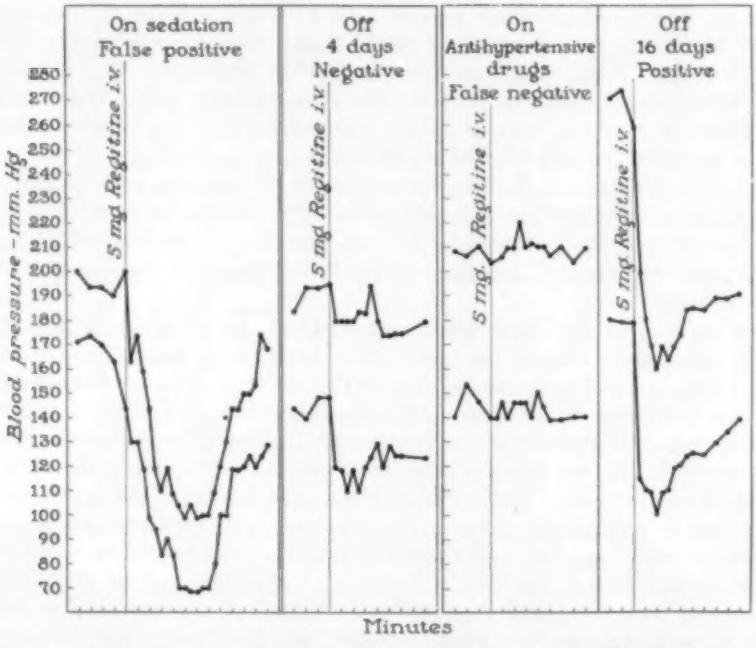


FIGURE 2: False positive and false negative results of tests with regitine. *Left:* Observations made during sedation. The precipitous fall in blood pressure of a patient with hypertension after injection of regitine seems to indicate the presence of a pheochromocytoma, but 5 days after sedation was discontinued results were negative. *Right:* The blood pressure after the intravenous injection of regitine while the patient was receiving the antihypertensive drug, hydralazine hydrochloride (apresoline). After administration of apresoline was discontinued for 16 days, the blood pressure fell precipitously after the injection of regitine. This indicates a pheochromocytoma and the tumor was found at operation.

clinician. More than one test should always be carried out before an operation is performed.

Precautions: Before any of these tests are carried out, the use of any sedative or narcotic should be prohibited for at least 48 hours, and all self-medication should be checked. If these precautions are not taken, the pharmacologic tests may yield false positive results.

In the patients with paroxysmal hypertension sedatives inhibit the rise of the blood pressure during the cold pressor test which is the measuring stick. As a result the rise of the blood pressure during the histamine test may be greater than during the cold pressor test, thus indicating the presence of a tumor which does not exist. In patients with sustained hypertension, potassium thiocyanate, barbiturates, meperidine hydrochloride (demerol), morphine, chloral hydrate and probably many other sedatives may cause a fall in blood pressure after the intravenous administration of regitine when no tumor is present, and this fall may be similar to that produced by regitine in the presence of a pheochromocytoma. Shock seems greater in the patient who has had sedation and no tumor than in the patient with pheochromocytoma and no sedation although the decrease in blood pressure may be the same (Figure 2).

In addition to these drugs a marked difference in the blood pressure of the two arms occasionally may be responsible for false positive results in either the histamine or regitine test. In one of our patients with paroxysmal hypertension the basal systolic blood pressure varied 52 mm. of mercury and the diastolic blood pressure 38 mm. in the two arms. In order to have a positive result from the histamine test the blood pressure on the side of the higher basal blood pressure should rise considerably more after administration of histamine than during the cold pressor test on that same side. If the blood pressure during the cold pressor test was determined on the arm with the lower basal blood pressure and the blood pressure after injection of histamine was determined in the opposite arm a false positive result would be obtained. By measuring the blood pressure in both arms simultaneously during the histamine test, we found that the response to histamine was negative for pheochromocytoma.

In one of our patients with sustained hypertension the blood pressure which was measured in the arm with the higher pressure decreased 80 mm. systolic and 40 mm. diastolic after the intravenous injection of regitine. This could easily have been interpreted as a positive reaction to pheochromocytoma. However, this decrease only equalized the pressures in the two arms. When the blood pressures were determined simultaneously in the two arms, there was little or no fall in the blood pressure in either arm following the intravenous injection of 5 mg. of regitine. If a tumor had been present, a pronounced fall would have occurred on both sides. Therefore, we measure the blood pressure routinely in both arms of all patients, and if there is any disparity, the blood pressure is determined simultaneously in both arms during pharmacologic tests.

Various antihypertensive drugs may produce false negative results in the tests. Since most of the antihypertensive drugs are longer acting

(Figure 2) than the sedatives which produce false positive results, the difficulties are greater. We have had two patients who were taking antihypertensive drugs in whom tumors have been found although the initial test with regitine was negative, but after administration of the antihypertensive drug was discontinued for 8 to 16 days, positive results were obtained with regitine before operation.

Results: By close observation to these various difficulties during the last 10 years, we have carried out 9,616 pharmacologic tests on 8,665 patients, and we have found 61 pheochromocytomas in 51 patients. The diagnosis has been proved correct at operation. No untoward effects or deaths have occurred in any of these patients during the tests before operation, during operation or immediately after operation.

At this time we should like to report a case of pheochromocytoma and active progressive tuberculosis with cavitation of the left upper lobe of the lung.

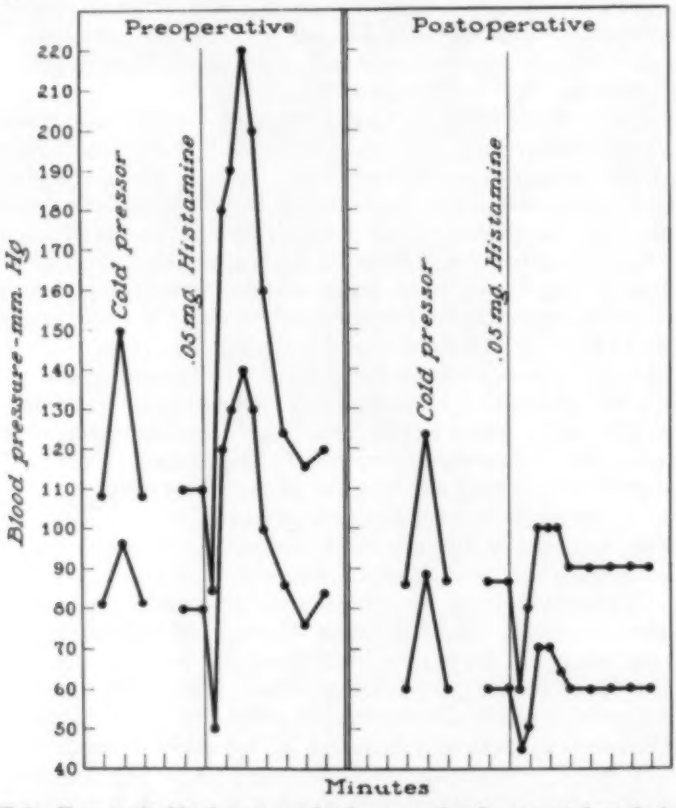


FIGURE 3: Changes in blood pressure in the case of pulmonary tuberculosis. *Left:* The preoperative increase in blood pressure during the cold pressor test and after the intravenous administration of histamine. Two minutes later regitine was given and the blood pressure decreased. *Right:* Increase in blood pressure during the cold pressor and histamine tests after removal of pheochromocytoma.

Report of Case of Tuberculosis

A 39 year old married man gave a history of headaches which awakened him at night. The headaches occurred particularly when he slept on his left side. At first cramping pains began in his legs; these were followed by pulsating pain which progressed up to the back of his neck and localized in the top of his head where it became a sharp throbbing pain. It caused him to sit up in bed feeling weak and at times he would have a sensation of smothering with trembling of his hands. During this episode his heart pounded but bradycardia rather than tachycardia seemed to be experienced by the patient. The headaches would last 5 to 10 minutes and then would disappear. They occurred about once a week. Occasionally he would have similar episodes without the headache during the day. For a period all attacks were relieved by phenobarbital.

Seven months after the first headache active extensive pulmonary tuberculosis of the left upper lobe with cavitation was discovered and sanatorium care was started. The patient was given streptomycin three times a week and 24 tablets of para-aminosalicylic acid (PAS) daily for 2 months with questionable improvement.

The headaches returned and became his chief complaint. Two months after admission to the sanatorium he had one particularly severe headache, which lasted from 9:30 p.m. to 9:30 a.m. the next day, was accompanied by nausea, vomiting, pallor, weakness and dizziness, and was not relieved by codeine. He then left the sanatorium and sought further diagnostic aid at the Mayo Clinic.

On admission to the clinic the patient stated that he had been an alcoholic for five years but had voluntarily discontinued drinking during the past year because of his daughter's accidental death. Aside from active tuberculosis his chief complaint was severe headache which usually occurred at night. During the few days he was in the hospital in Rochester, blood pressure was not observed except for the initial reading because of the absence of headache.

Neurologic examination gave negative results, and no cause for the headaches was found. The neurologist, Dr. Eaton, however, suggested that tests for pheochromocytoma should be carried out (Fig. 3). The response to histamine was positive and because of the excessive increase in blood pressure, regitine was given. Again the reaction was positive for pheochromocytoma. Removal of the tumor was suggested, but since it was close to the holiday season, the patient decided to go home for a time before operation.

When he returned 2 months later, the pulmonary tuberculosis has progressed, and cavitation had appeared in the right lung. Medical treatment was instituted for 2 weeks. During this time an excretory urogram revealed increased density in the right suprarenal region with ptosis of the right kidney.

At operation a pheochromocytoma, weighing 52 gm., was removed from the right adrenal gland. Levarterenol bitartrate (norepinephrine) was administered frequently to maintain the blood pressure at a normal level for 12 hours after operation; otherwise the postoperative course was uncomplicated. The patient obtained complete relief from headaches and gained 10 pounds in the next 7 weeks in spite of the extensive pulmonary condition. He then returned to the state sanatorium. He lived for 2 more years with no further headaches but finally died from pulmonary tuberculosis.

Comment

In four of our patients who gave a history of headache produced while they were lying on the left side, the pheochromocytoma has been found on the opposite side.

A search of the literature has disclosed only one case of tuberculosis and pheochromocytoma.[7] In this case the tuberculosis was healed. The pulmonary condition of our patient was so active and so extensive and he was so ill that pheochromocytoma might have been overlooked.

It is not likely that many patients with tuberculosis will have pheochromocytoma; however, since pharmacologic tests for pheochromocytoma can be carried out easily, it might be advisable to use them on any patient with tuberculosis and severe headaches. Although removal of the pheochromocytoma did not improve the pulmonary tuberculosis of our patient, his general condition was improved with the relief of the headaches and

he gained 10 pounds in the next 7 weeks in spite of his pulmonary condition and he lived comfortably for 2 more years.

SUMMARY AND CONCLUSIONS

1. It is not likely that many patients with tuberculosis will have pheochromocytomas in the adrenal gland; however, since pharmacologic tests for pheochromocytoma can be carried out easily, it might be advisable to use them on any patient who has tuberculosis and severe headaches, as in the patient reported on in this paper.

2. Although intrathoracic pheochromocytomas are rare, physicians and surgeons interested in thoracic diseases should be aware of the hazards of such tumors and the desirability of correct diagnosis before operation.

3. Pharmacologic tests with histamine or regitine for pheochromocytoma can be done quickly and without hazard if proper precautions are taken, particularly the avoidance of premedication. No untoward reactions or fatalities have occurred with any of these tests at the Mayo Clinic.

4. The preoperative diagnosis of pheochromocytoma can be made with the aid of these tests and their use will prevent fatalities or reactions due to the unexpected finding of a pheochromocytoma during removal of a paravertebral tumor from the thorax.

5. Although removal of the pheochromocytoma in the patient herein described, whose pulmonary condition was active and extensive, did not affect his pulmonary tuberculosis, his general condition was improved. Relief of the headaches was obtained and he gained 10 pounds in the next 7 weeks. He lived comfortably for 2 more years.

RESUMEN

1. No es posible qué muchos enfermos de tuberculosis padezcan de feocromocitoma de la suprarrenal; sin embargo, puesto que las pruebas farmacológicas del feocromocitoma pueden llevarse a cabo con facilidad, sería aconsejable usarlas en los enfermos que tienen tuberculosis y dolores intensos de cabeza, como en el caso del enfermo aquí presentado.

2. Aunque los feocromocitomas intratorácicos son raros los médicos y cirujanos interesados en afecciones del tórax deben estar alertas ante los peligros de tales tumores y tener presente cuán deseable es tener un diagnóstico correcto antes de la operación.

3. Las pruebas farmacológicas con histamina o regitina para el feocromocitoma pueden hacerse prontamente y sin peligro si se toman las precauciones adecuadas, especialmente el evitar la premedicación. No se han visto reacciones severas o fallecimientos usando estas pruebas en la Clínica Mayo.

4. El diagnóstico preoperatorio del feocromocitoma puede hacerse con la ayuda de estas pruebas y su uso puede evitar muertes o reacciones debidas a inesperado encuentro de un feocromocitoma durante la extracción de un tumor paravertebral del tórax.

5. Aunque la extirpación de un feocromocitoma en el enfermo aquí pre-

sentado, cuya condición pulmonar era activa y extensa, éso no afectó la tuberculosis pulmonar y sus condiciones generales mejoraron. Se obtuvo el alivio de su cefálea y aumentó 10 libras en las siguientes 7 semanas. Vivió de modo confortable por dos años más.

RESUME

1. Il est peu probable que beaucoup de malades, atteints de tuberculose, aient un phéochromocytome de la glande surrénale; cependant, puisque les tests pharmacologiques du phéochromocytome peuvent aujourd'hui être facilement pratiqués, il serait judicieux de les utiliser chez tout malade qui est atteint de tuberculose et de maux de tête sévères, copme chez le malade dont les auteurs rapportent l'observation.

2. Bien que les phéochromocytomes intrathoraciques soient rares, les médecins et chirurgiens qui s'intéressent aux affections thoraciques devraient être prévenus des possibilités de telles tumeurs, et de la nécessité d'établir un diagnostic correct avant l'opération.

3. Les tests pharmacologiques à l'histamine ou à la "régitine" peuvent être faits rapidement et sans risque d'erreur si les précautions adéquates sont prises, particuliérement si l'on évite un traitement antérieur. Aucune réaction secondaire ou accident n'est survenu avec ces tests à la Clinique Mayo.

4. Le diagnostic préopératoire de phéochromocytome peut être fait grâce à ces tests et leur emploi évitera les accidents ou les réactions dûs à la constatation inattendue d'une telle tumeur lors de l'exérèse d'une masse thoracique à siège paravertébral.

5. Bien que l'extirpation du phéochromocytome chez le malade dont l'observation est rapportée ne modifiât pas sa tuberculose pulmonaire qui était en pleine évolution, l'état général fut amélioré. Le soulagement des maux de tête fut obtenu, et le malade reprit dix livres dans les sept semaines suivantes. Il survécut dans de bonnes conditions encore pendant deux ans.

ZUSAMMENFASSUNG

1. Es ist nicht wahrscheinlich, dass viele Patienten mit einer Tuberkulose ein Phaeochromocytom in den Nebennieren haben werden; da sich aber pharmakologische Teste auf Phaeochromocytome leicht ausführen lassen, dürfte es ratsam erscheinen, sie bei jedem Patienten anzuwenden, der eine Tuberkulose hat und an schwerem Kopfweh leidet, so wie bei dem Patienten, über den in dieser Arbeit berichtet wird.

2. Obwohl intrathorakale Phaeochromocytome selten sind, müssen Internisten und Chirurgen, die an Thoraxerkrankungen interessiert sind, Bescheid wissen über die Gefahren solcher Tumoren und dass die korrekte Diagnose vor der Operation wünschenswert ist.

3. Pharmakologische Teste mit Histamin oder Regitin auf Phaeochromocytome können schnell und ohne Wagnis ausgeführt werden, wenn entsprechende Vorsichtsmassregel getroffen werden, besonders eine Vorbehandlung vermieden wird. Es haben sich aber keine ungünstigen Re-

aktionen oder Todesfälle mit einer dieser Proben an der Mayo-Klinik ereignet.

4. Die praeoperative Diagnose auf Phaeochromocytome kann mit Hilfe dieser Teste gestellt werden und ihre Anwendung wird Todesfälle und solche Reaktionen verhindern, die die Folge des unerwarteten Vorfindens eines Phaeochromocytoms während der Entfernung eines paravertebralen Tumors aus dem Thorax sind.

5. Obwohl die Entfernung des Phaeochromocytoms bei den hier beschriebenen Patienten, dessen Lungenprzess aktiv und ausgedehnt war, keinen Einfluss auf seine Lungentuberkulose ausübte, wurde sein Allgemeinzustand gebessert. Befreiung von den Kopfschmerzen wurde erzielt, und er nahm in den folgenden 7 Wochen 10 Pfund zu. Er führte während der nächsten 2 Jahre ein angenehmes Leben.

REFERENCES

1 Roth, G. M. and Kvale, W. F.: "Pheochromocytoma, Factors in the Accurate Pharmacologic Diagnosis," *Dis. Chest*, 29:366, 1956.

2 Roth, G. M. and Kvale, W. F.: "A Tentative Test for Pheochromocytoma," *Am. J. M. Sc.*, 210:653, 1945.

3 Emlet, J. R., Grimson, K. S., Bell, D. M. and Orgain, E. S.: "Use of Piperoxan and Regitine as Routine Tests in Patients With Hypertension," *J.A.M.A.*, 146:1383, 1951.

4 Gifford, R. W., Jr., Roth, G. M. and Kvale, W. F.: "Evaluation of New Adrenolytic Drug (Regitine) as Test for Pheochromocytoma," *J.A.M.A.*, 149:1628, 1952.

5 Hines, E. A., Jr. and Brown, G. E.: "A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State," *Ann. Int. Med.*, 7:209, 1933.

6 Roth, G. M., Hightower, N. C., Jr., Barker, N. W. and Priestley, J. T.: "Familial Pheochromocytoma: Report on Three Siblings With Bilateral Tumors," *A.M.A. Arch. Surg.*, 67:100, 1953.

7 Kelly, H. M., Piper, M. C., Wilder, R. M. and Walters, W.: "Case of Paroxysmal Hypertension With Paraganglioma of the Right Suprarenal Gland," *Proc. Staff Meet., Mayo Clin.*, 11:65, 1936.

The Use of Noscapine (Narcotine) as an Antitussive Agent*

MAURICE S. SEGAL, M.D., F.C.C.P.,‡ MERRILL M. GOLDSTEIN, M.D.** and ERNEST O. ATTINGER, M.D.***

Boston, Massachusetts

The pharmacologic effects of Noscapine† (Narcotine discovered by Rabiquet in 1817) have been studied for many years.[3] Recently it has been demonstrated to be significant in preliminary clinical trials.[4] Noscapine is the second most abundant alkaloid in opium, next to morphine. Its empirical formula is $C_{22}H_{23}O_7N$.

Actually Noscapine bears little resemblance to the narcotic alkaloids, either chemically or pharmacologically. The structure of morphine, codeine, and similar compounds is based on a phenanthrene nucleus, whereas Noscapine is an isoquinoline derivative (related to papaverine). It is readily absorbed after oral or parenteral administration, disappears rapidly from the blood stream, and only traces appear in the urine. Its fate is unknown. It has been referred to as the least toxic of the opium alkaloids in mice, rats, and man. Up to 3 grams by mouth have been given to man with only minor side reactions. Chronic toxicity studies did not demonstrate any cumulative effects. No depressant action on respiration or the central nervous system has been observed up to toxic doses; stimulation may appear with higher doses. The effects of Noscapine on the gastrointestinal tract were insignificant. No effects on secretory activity and minimal effects on gastrointestinal movements were reported. Occasionally emesis and constipation were noted only with large doses. No significant analgesic action was observed. Potentiation of morphine analgesia with antagonism to side effects have been reported, but not definitely established. The parenteral use of Noscapine has been limited because of local pain. In experimental cough in animals and man, it was described as effective as codeine. No tolerance to the drug developed. Finally, although no antihistaminic action was found, it did inhibit the "allergic cough" in sensitized guinea pigs exposed to aerosols of specific antigen. It did not, however, prevent anaphylactic shock after injected antigen. In a study centering about the experimental production of cough in normal and asthmatic subjects, small doses of Narcotine (5 and 15 mg.) were demonstrated to have greater anti-

*From the Department of Medicine, Tufts University School of Medicine and the Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital.

‡Clinical Professor of Medicine, Tufts University School of Medicine and Director, Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital.

**Clinical Instructor assigned Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital.

***Assistant Professor in Medicine assigned Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital.

†Nectadon, brand of Noscapine, kindly supplied by Merck Sharp and Dohme, was employed in these studies.

tussive activity (suppression of cough response to citric acid aerosols) than the 30 mg. codein.[4]

Clinical Studies

Fifty-one patients with cough due to various types of pulmonary disease were placed on a program of Noscapine therapy in an attempt to evaluate its effectiveness as an antitussive agent.[5] The vital statistics of each of these patients are summarized in Table I.* The diagnoses included the following: acute bronchitis, allergic and non-allergic; tracheobronchitis; chronic bronchial asthma; chronic pulmonary emphysema; bronchiectasis; and pulmonary neoplasms.

In this group of patients, there were 27 women and 24 men, with ages ranging from 17 to 75 years. Most of them fell within the age range of 31 to 70 years. The duration of the cough varied from one week to 30 plus years.

The dosage of Noscapine varied according to the individual's needs for antitussive therapy. Seventeen received 15 to 30 mg. as a single bedtime dose. The remaining 34 received 15 to 60 mg. from two to six times daily. The relationship of dose to effect was graded from 0 to 4+ (Table II).

The overall results were graded from 0 to 4+ employing careful objective as well as subjective estimates of the degree of cough suppression (Table II).

TABLE II

NOSCAPINE (P.O.)

Relation of Dose to Effect			Grade of Response					
Dose (Mgm.)	Time Adm.	Trials	0	1+	2+	3+	4+	
15	HS	2	—	—	1	1	—	
15	BID	1	—	—	—	1	—	
15	TID	5	1	—	—	4	—	
15	4ID	1	—	—	—	—	1	
30	HS	14	1	4	3	4	2	
30	TID	4	—	—	—	3	1	
30	4ID	3	—	—	—	2	1	
30	6ID	12	1	1	5	3	2	
60	4ID	10	—	—	10	—	—	
60	6ID	2	—	—	1	1	—	
		54	3	5	20	19	7	
			(6)	(9)	(37)	(35)	(13)	% Response

*Table I omitted because of length, will appear in reprints.

TABLE III

NOSCAPINE (P.O.)
Comparison with Other Antitussive Agents—30 Trials

	Less	Same	Better
Dihydrocodeinone bitartrate	1	3	2
X-71	2	5	4
Codeine	—	1	3
Dilaudid	1	—	—
Diphenhydramine-aminophyllin	3	—	5

TABLE IV

SIDE EFFECTS — 54 TRIALS

Side effects:	Drowsiness: 3 Difficulty in raising secretions: 2 Headache: 1 None: 45
Loss of effect:	In 3

A comparison with other antitussive agents was attempted in 30 trials. This data appears in Table III. The side effects and loss of effectiveness are also recorded in Table IV.

Discussion

Fifty out of 54 trials with Noscapine in 51 patients revealed beneficial effects graded from 1+ to 4+. Thus the effectiveness of this antitussive agent was observed in 94 per cent of those treated. However, the most significant effects were observed in the group with 3 to 4+ suppression. This constitutes 26 trials out of the group—(48 per cent), (Table II).

A comparison of the relative effectiveness of Noscapine with dihydrocodeinone, X-71, codeine, dilaudid, and diphenhydramine-aminophyllin (hydryllin) revealed the following: Less effectiveness in seven of 30 trials; no further changes in nine of 30 trials; and significant improvement was noted with Noscapine over the other antitussive agents in 14 of 30 trials (Table III).

There were no side effects in 45 of those treated. However, drowsiness was noted in three, difficulty in raising secretions in two, and headache in one. A gradual loss of effectiveness was observed in three. The nature of this loss of effect could not be determined.

CONCLUSIONS

1. In clinical studies, Noscapine administered orally in doses of 15 to 60 mg. at graded intervals proved effective as an antitussive agent in 94 per cent of 54 trials in 51 patients who were treated for cough due to various types of bronchopulmonary disease. Its maximum effectiveness

(3 to 4+ cough suppression), however, was noted in 48 per cent of the overall group.

2. In 23 out of 30 trials, (77 per cent), comparable or better effects were observed with Noscapine when compared with other antitussive agents.

3. There were no side effects noted in 45 persons treated with Noscapine. Moderate drowsiness was observed in three patients; difficulty in raising secretions in two; headache in one. A gradual loss of effectiveness was observed in three cases. No gastrointestinal complaints or respiratory depression was noted in any of the cases receiving Noscapine.

CONCLUSIONES

1. Según los estudios clínicos, la Noscapina por vía oral a la dosis de 25 a 60 miligramos con intervalos graduales, se mostró efectiva como agente béquico en el 94 por ciento en el grupo 51 enfermos en los que se hicieron 54 ensayos, entre enfermos de diversos padecimientos broncopulmonares.

La efectividad máxima sin embargo (3 a 4 + de supresión de tos), se notó en 48 por ciento del conjunto.

2. En 23 de 30 ensayos (77 por ciento) se observaron efectos comparables o mejores, de la Noscapina frente a otros agentes béquicos.

3. No hubo efectos colaterales en 45 personas tratadas con Noscapina. Moderada somnolencia en 3 enfermos; dificultad para expulsar las secreciones en dos, dolor de cabeza en uno. Se observó pérdida gradual de eficacia en tres. No hubo molestias gastrointestinales ni depresión respiratoria en ninguno de los casos estudiados.

RESUME

1. Au cours d'études cliniques, la "Noscapine"; administrée par la bouche aux doses de 15 à 60 mmgr. à intervalles également espacés, s'est montrée efficace, contre la toux imputable à différentes sortes d'affections bronchopulmonaires, dans 94% des 54 essais pratiqués chez 51 malades. Son maximum d'efficacité cependant, fut notée dans 48% du groupe total.

2. Dans 23 cas sur 30 essais (77%) des effets comparables ou meilleurs que ceux d'autres sédatifs de la toux furent observés avec la Noscapine.

3. On ne nota aucun effet secondaire chez 45 personnes traitées par la Noscapine. On observa un peu de somnolence chez trois malades; de la difficulté à expectorer chez deux; des maux de tête chez un malade. On nota dans trois cas une perte progressive de l'efficacité du produit. Il n'y eut de complications gastrointestinales ou de diminution de la fonction respiratoire dans aucun des cas traités.

SCHLUSSFOLGERUNGEN

1. Bei klinischen Versuchen erwies sich Noscapin bei oraler Zuführ in Mengen von 15-60 mg. in abgestuften Intervallen als ein wirksames hustenstillendes Mittel in 94% von 54 Proben an 51 Kranken, die in Behandlung standen wegen Husten als Folge verschiedener Typen von Bronchopulmonalen Erkrankungen. Seine maximale Wirksamkeit (3-4 +

Hustenunterdrückung) wurde in 48% der gesamten Gruppe beobachtet.

2. Unter 23 von 30 Prüfungen (77%) wurden vergleichbare oder bessere Wirkungen festgestellt mit Noscapin im Vergleich mit anderen hustenstillenden Mitteln.

3. An 45 mit Noscapin behandelten Personen wurden keine Nebenwirkungen bemerkt. Mässige Schläfrigkeit machte sich bei 3 Kranken bermerkbar; Schwierigkeiten, das Sekret abzuhusten, bei 2 Kranken; Kopfweh in einem Fall. Ein allmählicher Verlust der Wirksamkeit wurde in 3 Fällen beobachtet. Es kam zu keinen gastrointestinalen Schwierigkeiten oder respiratorischer Schwächung bei irgend einem der mit Noscapin behandelten Fälle.

REFERENCES

1 Segal, M. S.: *The Management of the Patient with Severe Bronchial Asthma.* Springfield, Ill., Charles C Thomas, 1950.

2 Segal, M. S. and Dulfano, M. J.: *Chronic Pulmonary Emphysema. Physiopathology and Treatment.* New York, Grune and Stratton, Inc., 1953.

3 Winter, C. A.: *Narcotine—An Antitussive Agents for Investigational Use.* Publication Medical Division Sharp and Dohme Division of Merck & Co., Inc. July, 1954.

4 Bickerman, H. A. and Barach, A. L.: "The Experimental Production of Cough in Human Subjects Induced by Citric Acid Aerosols. Preliminary Studies on the Evaluation of Antitussive Agents," *Am. J. Med. Sc.*, 228:156, 1954.

5 Segal, M. S. and Attinger, E. O.: "Chronic Pulmonary Emphysema—Symptomatic Therapy," *Medical Records and Annals*, 50:42, 1956.

A Method of Desensitization of Allergy Due to Streptomycin with Prednisone

SUSHIL CHAKRAVARTY, M.D., F.C.C.P.*
Philadelphia, Pennsylvania

Lowell[1] gave the incidence of allergy to streptomycin as 10 per cent. This high incidence is due to administration of the drug for long periods in tuberculosis. Most of the allergic reactions were not serious. There was no way of knowing whether a patient allergic to streptomycin could react again on re-administration. It might be assumed that he would. Houghton[2] in England and Chakravarty[3] in this country described two individual methods of desensitizing streptomycin allergy by ACTH and cortisone.

This presentation discusses the method by which four patients who were allergic to streptomycin could tolerate this drug after desensitization with prednisone.

When streptomycin with paraaminosalicylic acid (PAS) and/or isoniazid were given it was difficult to determine which of the drugs was causing allergy. For this purpose, an intradermal skin test with 10 mg. of streptomycin in 0.1 ml. of normal saline was given in one forearm. If there was induration of 5 to 10 mm. in diameter, the reaction was read as 1+, if 11 to 20 mm., it was 2+ and if more than 20 mm. or necrosis, it was 3+. If induration was less than 5 mm., it was read as doubtful and if no induration, but only erythema, it was considered negative.

The skin test generally became positive within 12 to 24 (occasionally 48) hours.

Simultaneously, with the streptomycin skin test in one forearm, purified protein derivative (PPD) No. 1 was given in the other.

Generally, both streptomycin skin test and PPD tests were positive in allergic cases. Prednisone was started after the skin tests were known. The dosage varied in some cases, but the following dosage schedule was followed:

For one week 50 mg. of prednisone was given orally each day. This was given in three divided doses. Then streptomycin skin test and the first dose of purified protein derivative No. 1 were repeated. Usually either the streptomycin skin test was negative or the reaction was much less than before. In cases with the streptomycin skin test still positive, prednisone was given for another week before streptomycin was started.

When the skin reactions were diminished at the end of one week, with prednisone, streptomycin was started intramuscularly, 10 mg. on the first day and doubled every day until it reached 800 mg. Then 1.0 gm. twice weekly. Patients reached 1.0 gm. of streptomycin on the ninth day.

*From the Department of Chronic Diseases of the Chest, Philadelphia General Hospital. Presently at the V. P. Chest Institute, Delhi University.

After 1.0 gm. of streptomycin was administered twice weekly for four weeks, prednisone was tapered off and stopped in about two weeks.

Before stopping prednisone, every patient was given 20 units of ACTH intramuscularly daily. This was gradually tapered off and stopped in eight days. ACTH was given to stimulate the adrenal cortex. The last four days of prednisone was combined with ACTH. This was given so that the adrenals had sufficient time to be stimulated and if there was any infection, in the meantime, prednisone would help, as the adrenal cortex was probably not stimulated fully in the first four days.

In this series, 150 patients were tested with streptomycin skin test of whom 12 were allergic clinically. Eleven allergic cases reacted to streptomycin skin test but one did not. The 138 who were getting streptomycin but were not allergic clinically were negative to streptomycin skin test.

During prednisone therapy these allergic patients were negative both to streptomycin skin test and PPD No. 1. When desensitization was done, reaction to PPD No. 1 gradually became positive but streptomycin skin test remained negative. This showed that desensitization was complete.

Unlike penicillin reaction, which was immediate, streptomycin skin test gave a delayed reaction, like tuberculin. This could be seen also from allergic rashes due to streptomycin. These rashes were of erythema and induration type. This type of reaction was due to the *specific necrotising antibody factor* or *cellular sensitizing antibody*. In this type of reaction sensitivity to the agent could not be transferred by serum as in immediate type of reaction, but could be transferred by certain cells from the sensitized subject. In immediate type, it was the release of histamine that caused the allergic reaction. The type of antibody was Reagin.

Case 1: This 47 year old white man was admitted with bilateral pulmonary tuberculosis, on October 25, 1955. He was treated with streptomycin 1.0 gm. twice weekly and PAS 12 gm. daily from October 28, 1955. On November 6, he had maculopapular rashes and pruritus all over the body. On November 8, he had severe angioneurotic edema.

Haughton's method of desensitization was tried and 80 units of ACTH was given intramuscularly daily until all edema and rashes cleared. Benadryl, 50 mg. intramuscularly thrice daily was also given. After six days, all edema and rashes subsided.

Houghton recommended for desensitization: 80 units of ACTH intramuscularly. It should be given in divided doses with the full dose of the drug the patient was receiving prior to allergic manifestation, after all rashes and pruritus subsided.

Accordingly, on November 18, along with 80 units of ACTH intramuscularly, 1.0 gm. streptomycin and 300 mg. isoniazid were given. Para-aminosalicylic acid was not given as it was thought he might also be allergic to PAS, so the treatment was modified.

After one day, he broke down again in macular rashes and angioneurotic edema followed by exfoliative dermatitis. So all drugs were stopped except ACTH and 80 mg. daily of oral prednisone in divided doses was added. This was continued until November 24, when ACTH was stopped and only 80 mg. of prednisone orally was given.

Streptomycin skin test and PPD No. 1 were done on December 1955. Both were negative. On December 6, he was started with streptomycin intramuscularly as described above.

After Houghton's method failed to desensitize the allergy due to streptomycin, our method was tried.

Prednisone was given until February 6, 1956. After that, he was given ACTH to stimulate the adrenal cortex. He has tolerated streptomycin even without prednisone, since February 6, 1956. This patient is an example of severe allergic reaction and he was given high doses of prednisone for ninety days which is longer than usual.

Case 2: This 57 year old colored man had been treated with streptomycin 1.0 gm. twice weekly and isoniazid—300 mg. daily since August 18, 1955 for far advanced pulmonary tuberculosis. On January 8, 1956, he had pruritus and erythematous papular eruptions all over the trunk of his body.

Both streptomycin and isoniazid were stopped. When all rashes subsided isoniazid was started and the full dose, 300 mg. daily was tolerated. On February 13, 1956 he was restarted on streptomycin, 1.0 gm. but he broke into generalized rashes and itching. When all rashes subsided, it was decided to start para-aminosalicyiic acid, 12 gms. daily, so he would be treated with INH and PAS. On February 18, 1956, he was started on 12 gm. of PAS but he had a rise in temperature to 104° F. and rashes all over the body. After all rashes subsided, he tolerated isoniazid well.

At this time it was decided to desensitize. He was skin tested on March 12, 1956. Streptomycin skin test was negative but PPD No. 1 was 1+.

He was desensitized with prednisone, but began itching when the dose was reduced to 10 mg. daily. This was controlled with pyribenzamine 100 mg. thrice daily.

He received prednisone for 50 days and was given ACTH after prednisone, as described in the method. He has tolerated streptomycin 1.0 gm. twice weekly for about four weeks after both prednisone and ACTH were stopped.

Cases 3 and 4 were desensitized by the same method as was used in Case 2.

SUMMARY

1. In the treatment of tuberculosis, allergy due to streptomycin is found in 10 per cent of cases.

2. To identify such allergy, intradermal skin test with 10 milligram streptomycin in 0.1 ml. normal saline is done. Among 150 patients 12 were allergic clinically. Of these 12 patients, 11 (90.7 per cent) reacted to streptomycin skin test. The rest of 138 patients who were not allergic clinically to streptomycin gave negative reactions to skin test.

3. The streptomycin skin test is a delayed type of reaction, which becomes positive in 12 to 24 hours.

4. To desensitize, 50 milligrams of prednisone is given orally daily for one week. After a week, along with 50 mg. prednisone daily streptomycin is given intramuscularly, starting with 10 mg. on the first day and doubled daily up to 800 milligrams. Then 1.0 gram of streptomycin is administered twice weekly. After 1.0 gram has been given twice weekly for four weeks, prednisone is tapered off and stopped, in about two weeks.

5. Before stopping prednisone 20 units of ACTH is given daily intramuscularly. ACTH is gradually tapered off and stopped in eight days.

6. Among four patients allergic to streptomycin and desensitized, three were positive to the first dose of purified protein derivative, one could not be tested due to angioneurotic edema. During prednisone administration all were negative to the same dose of PPD. Four weeks after prednisone was stopped, all were again positive to PPD.

This study was possible by the liberal supply of meticorten (prednisone) supplied by Schering Corporation. I wish to thank George Babcock, Jr., M.D. for his assistance and cooperation.

RESUMEN

1. Se encuentra la alergia a la estreptomicina en 10 por ciento de los casos.

2. Para reconocer tal alergia se hace la reacción intradérmica con 10 ml. de estreptomicina en 0.1 ml. de solución salina isotónica. Entre 150 enfermos, 12 eran alérgicos clínicamente.

De estos 12 enfermos, 11 (90.7 por ciento) reaccionaron al a prueba cutánea. El resto, 138 enfermos que no eran clínicamente alérgicos dieron reacciones cutáneas negativas.

3. La reacción cutánea a la estreptomicina es retardada y se hace positiva a las 12 o 24 horas.

4. Para obtener la desensibilización se dan 50 ml. de prednisona oralmente, diariamente por una semana. Después de una semana se da además, junto con la prednisona, estreptomicina intramuscular empezando con 10 mg. en el primer día y doblando la dosis diariamente hasta 800 ml. Desde entonces se da 1 gm. dos veces por semana. La prednisona se va disminuyendo y se suprime al cabo de dos semanas.

5. Antes de suspender la prednisona se dan 20 unidades de ACTH diariamente intramusculares. La ACTH se disminuye gradualmente y se suspende al cabo de ocho días.

6. Entre los enfermos alérgicos a la estreptomicina y desensibilizados, tres eran positivos a la primera dosis de PPD, uno no pudo ser probado debido a edema angioneurótico.

Durante la administración de prednisona todos fueron negativos a la misma dosis de PPD. Cuatro semanas después de que la prednisona se suspendió todos volvieron a ser positivos a PPD.

RESUME

1. Dans le traitement de las tuberculose, on trouve une allergie à la streptomycine dans 10% des cas.

2. Pour indentifier une telle allergie, il convient de pratiquer un test cutané intradermique avec 10 ml. de streptomycine, dissous dans du sérum physiologique normal à 0,1 ml. Para 150 malades, 12 se montrèrent cliniquement allergiques Parmi ces 12 malades, II (90.7%) réagirent au test cutané à la streptomycine. Le reste des 138 malades qui n'eurent pas d'allergie clinique à la streptomycine eurent des réactions négatives au test cutané.

3. Le test cutané à la streptomycine provoque une réaction retardée qui devient positive en 12 à 24 heures.

4. Pour désensibiliser, on donne quotidiennement pendant une semaine, 50 ml. de "prednisone" par la bouche. Après une semaine, on peut utiliser la streptomycine par voie intramusculaire, en commençant par 10 mg. le premier jour, puis la dose est doublée chaque jour jusqu'à atteindre 800 ml. Alors 1 gramme de streptomycine est administré deux fois par semaine. Après une période de ce traitement pendant quatre semaines, la prednisone est diminuée arrêtée au bout de deux semaines.

5. Avant d'arrêter la "prednisone," on donne quotidiennement 20 unités d'ACTH par voie intramusculaire. L'ACTH est progressivement diminuée et arrêtée au bout de 8 jours.

6. Sur 4 malades allergiques à la streptomycine et désensibilisés, trois eurent des réactions positives à la première dose de dérivés purifiés. Un n'a pas pu être testé à cause de la survenue d'un oedème angio-neurotique. Pendant l'administration de la prednisone, tous eurent des réactions négatives avec la même dose de tuberculine purifiée. Quatre semaines après que la prednisone ait été cessée, tous eurent de nouveau des réactions positives.

ZUSAMMENFASSUNG

1. Bei der Behandlung der Tuberkulose findet man eine Streptomycin-Allergie in 10% der Fälle.

2. Um solche Allergie zu erkennen, wird ein intrakutaner Hauttest mit 0,1 Streptomycin in 0,1 normaler Kochsalzlösung vorgenommen. Von 150 Patienten waren 12 klinisch allergisch, von diesen 12 Patienten reagierten 11 (90,7%) auf den Streptomycin-Haut-Test. Der Rest der 138 Patienten, die klinisch nicht allergisch auf Streptomycin waren, hatten negativen Reaktionen ouf die Hautprobe.

3. Die Streptomycin-Hautprobe gehört zu dem Reaktionstyp mit Verzögerung, der nach 12-24 Stunden positiv wird.

4. Zwecks Desensibilisierung werden 0,5 Prednison oral täglich eine Woche lang gegeben. Nach einer Woche mit diesen 0,5 Prednison täglich wird Streptomycin intramuskulär gegeben beginnend mit 10 mg. am ersten Tag und täglicher Verdoppelung bis zu 0,8. Dann wird 1 gr. Streptomycin 2 mal wöchentlich verabfolgt. Nachdem 1 gr. 2 mal wöchentlich 4 Wochen lang gegeben worden ist, wird das Prednison allmählich verringert und nach ungefähr 2 Wochen ganz gestoppt.

5. Ehe mit dem Prednison aufgehört wird, werden 20 Einheiten ACTH täglich intramuskulär gegeben. Das ACTH wird schrittweise vermindert und in 8 Tagen damit aufgehört.

6. Von 4 gegen Streptomycin allergischen und desensibilisierten Patienten reagierten 3 positiv auf die erste Dosis PPD und einer konnte nicht getestet werden infolge enies angioneurotischen Oedems. Während der Prednison-Behandlung reagierten alle auf die gleiche Dosis PPD negativ. 4 Wochen, nachdem das Prednison abgesetzt worden war, reagierten alle wieder positiv auf PPD.

REFERENCES

1 Lowell, C. F.: "Allergic Reactions to Sulfonamide and Antibiotic Drugs," *Ann. Int. Med.*, 43:333, 1955.

2 Houghton, L. E.: "Combined Corticotrophin Therapy and Chemotherapy in Pulmonary Tuberculosis with Special Reference to Hypersensitive Reactions," *Lancet*, 1:595, 1954.

3 Chakravarty, S.: *The Place of ACTH and Cortisone in Therapy of Tuberculosis.* Antibiotics Annual 1955-56. P. 192. Medical Encyclopedia Inc., New York.

Patent Ductus Arteriosus with Pulmonary Hypertension: Temporary Obstruction of the Ductus During Cardiac Catheterization to Evaluate Indication for Surgical Closure

PAUL KEZDI, M.D., ROBERT R. J. HILKER, M.D. and PAUL SCHIMERT, M.D.
Chicago, Illinois

It was suggested in recent reports that a patent ductus arteriosus with pulmonary hypertension and partial reversal of the shunt may be closed if special precautions are undertaken during surgery.[1] In children the results seem to be more promising than in adults.[2] Based on experience with a limited number of cases, the general concensus of opinion is that closure of the ductus may be hazardous if, preoperatively, a right to left shunt can be demonstrated which exceeds the magnitude of the left to right shunt.[3, 4] However, the calculation of shunts using the Fick principle in the presence of bidirectional flow through the ductus is far from accurate. Such measures as 100 per cent oxygen breathing and intravenous priscoline injection are helpful tests to evaluate whether pulmonary vascular resistance can be lowered and the shunt reversed entirely to left to right.[5] The actual closure of the ductus cannot be predicted until thoracotomy and application of a clamp to the ductus with observation of the pulmonary and systemic pressures. It is said that closure of the ductus is hazardous if pulmonary artery pressure rises and systemic pressure decreases on occlusion.[3] However, thoracotomy in a patient with already markedly impaired cardiac and pulmonary function is a formidable procedure if it is decided not to close the ductus. The following is a report of two patients with patent ductus and pulmonary hypertension in whom the ductus was temporarily obstructed during cardiac catheterization, and changes in pulmonary artery and systemic pressure, and in the saturation of the femoral and pulmonary artery blood samples were observed to determine operability.

Method: Cardiac catheterization was performed in the usual fashion. The blood samples were analyzed in part by the method of Van Slyke and Neill, and in part by a cuvette oximeter. At each position at least one blood sample was examined by the cuvette and analyzed simultaneously by the Van Slyke technic to check the accuracy of the cuvette. Two or three additional cuvette readings were usually obtained and the results were averaged. Expired air for oxygen consumption was collected in a Tissot manometer and the samples analyzed by a Beckman oxygen analyzer. When the diagnosis of a patent ductus with pulmonary hypertension

From the Cardiopulmonary Laboratory, Wesley Memorial Hospital and Department of Medicine, Northwestern University Medical School.
This work was aided in part by the Lizzie K. Schermerhorn Memorial Fund.

and partial reversal of the shunt was established, the patient was recatheterized using a three-way catheter with an inflatable rubber balloon, as described by Brofman.[6] The catheter was maneuvered into the main pulmonary artery and through the patent ductus into the aorta. Following that, simultaneous pressures were recorded in the pulmonary artery and the aorta. Blood samples from the pulmonary artery and from the aorta or femoral artery were also obtained. The balloon was then inflated with the amount of diodrast previously determined to give the balloon a diameter of 15 mm. The catheter was then withdrawn under fluoroscopy control until it obstructed the patent ductus at the aortic side. Obstruction was assumed when the catheter resisted further moderate pull and transmission of the cardiac pulsations to the catheter could be felt. Constant moderate pull was maintained to hold the balloon in position. Following obstruction, simultaneous pulmonary artery and aortic pressures were recorded at one to three minute intervals. Several blood samples were obtained from the femoral artery or the aorta and from the pulmonary artery. 100 per cent oxygen breathing was administered and a final arterial blood sample obtained just before the obstruction was discontinued.

Case 1: A 22 year old white woman who came to Chicago Wesley Memorial Hospital for cardiac evaluation, was known to have heart disease since birth. There was no history of cyanosis, squatting, or heart failure. During childhood she was unable to play with children because of shortness of breath and tiredness. Her complaints gradually increased during the last two years. She could go up only one flight of stairs with difficulty. She was unable to help with light housework which she previously had

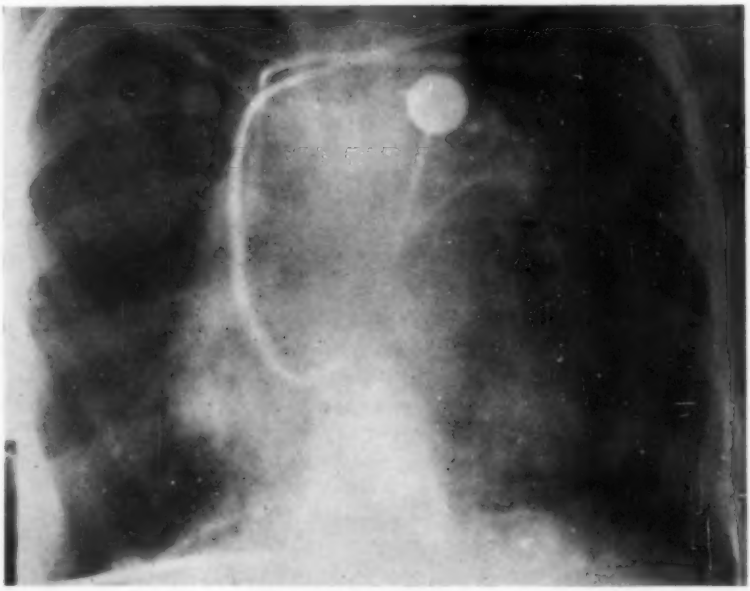


FIGURE 1: Catheter with the inflated balloon in the patent ductus. A second catheter placed into the left pulmonary artery.

done. Occasionally she coughed up blood. She never had ankle swelling.

On physical examination she appeared to be well-developed and well-nourished in no apparent distress at rest. Lungs were clear on percussion and auscultation. She had pigeon breast and kyphoscoliosis of the dorsal spine. The heart was enlarged to the right, while the left heart border was normal. There was an increase of the retrosternal dullness and increased right ventricular activity could be felt. A grade III harsh systolic murmur heard diffusely over the entire precordium on both the left and the right side of the sternum. It could be heard throughout systole, but no diastolic murmur was present. The fingernails were not clubbed and showed only a questionable bluish tinge. The blood pressure in the right and left arms was 118/80,

TABLE I

CARDIAC CATHETERIZATION FINDINGS

	Case No. 1				Case No. 2			
	Pressures s/d	mm. Hg. mean	Blood O, Vol. Per Cent	Saturation Per Cent	Pressures s/d	mm. Hg. mean	Blood O, Vol. Per Cent	Saturation Per Cent
PA	110/65	80	10.1	55	110/64	76	17.3	71
PVC	.....	8	....	....	.....	3	....	....
RV	110/3	38	8.9	49	112/4	....	16.4	67
RA	5/0	2	9.1	50	4/0	1	16.3	67
SVC	.....	....	8.9	49	.....	....	16.1	66
IVC	.....	....	....	....	.....	....	16.0	66
BA right	.....	....	16.3	89	.....	....	22.5	92
BA left	98/55	69	15.7	86	.....	....	....	....
FA	.....	....	15.2	83	.....	....	20.3	83
Aorta below ductus	110/60	....	....	....	105/65	78	19.8	81
Oxygen consumption cc./min.	198				192			
Total pulmonary flow	3.3 L/min.				3.7 L/min.			
Effective pul. flow	2.5 L/min.				3.0 L/min.			
Systemic flow below ductus	3.1 L/min.				4.6 L/min.			
L ⟶ R shunt	0.8 L/min.				0.7 L/min.			
R ⟶ L shunt	0.6 L/min.				1.6 L/min.			
Pulmonary arteriolar resistance	1743 dyn/sec/cm^{-5}				1594 dyn/sec/cm^{-5}			
Systemic resistance	1828 dyn/sec/cm^{-5}				1356 dyn/sec/$^{-5}$			

in the right leg it was 150/95. The electrocardiogram was compatible with right and left ventricular hypertrophy and strain. The x-ray film showed right ventricular hypertrophy and distention of the main stem pulmonary artery. No other selective cardiac chamber enlargement could be detected. However, because of the chest deformity, the findings were difficult to interpret. There was a diamond-shaped systolic murmur in the phonocardiogram and a good aortic second sound. The possibility of a subaortic stenosis was, therefore, entertained, although the brachial artery pulse tracing did not show delay of the pressure peak or an anacrotic notch. The cardiac catheterization findings revealed that this patient had a patent ductus arteriosus with pulmonary hypertension with partial reversal of the shunt (Table I). An angiocardiogram confirmed the diagnosis of a large patent ductus arteriosus.

She was then catheterized with the three-way catheter and the ductus was occluded by the previously described method for 20 minutes. Figure 1 shows the location of the three-way catheter with the balloon inflated and the patent ductus occluded. Since the proximal opening of the catheter became obstructed by a blood clot, a second catheter was introduced into the pulmonary artery. Figure 2 shows the pressure in the aorta and pulmonary artery following occlusion of the ductus. Table II gives the changes in pressures and in blood oxygen saturation. The findings indicate a significant increase of the pressure in the pulmonary artery, while the changes in the aortic pressure were minimal. The femoral artery oxygen saturation increased following occlusion. The continued low arterial oxygen saturation after occlusion was due to impaired oxygenation of the blood in the lung, since breathing 100 per cent oxygen increased the saturation to normal.

Despite these warning signs, surgery was performed with the intention of doing a partial closure of the ductus.[7] A large patent ductus was found entering the aorta just below a moderate infantile type of coarctation. Within three minutes of occlusion of the patent ductus with a clamp, a marked increase of the pulmonary artery pressure occurred, while the systemic pressure dropped. Before the clamp could be removed, the pulmonary artery ruptured. The rupture occurred in a small area which had been weakened by the surgical preparation. Despite the fact that the rupture was controlled, systemic hypotension developed and the condition of the heart deteriorated. She died in ventricular standstill with dilatation of the left ventricle. At autopsy a moderate subaortic stenosis was also found.

Case 2: This 30 year old white woman was known to have heart disease since early childhood. She never could keep up with her playmates. There was no history of

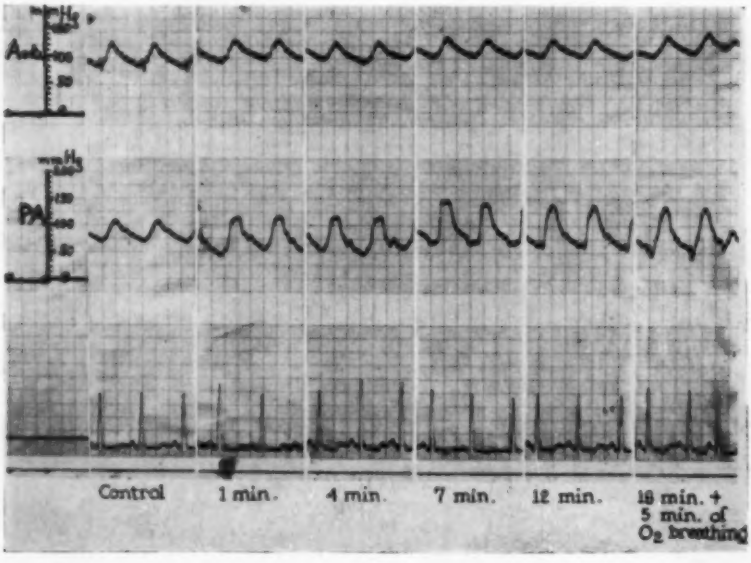


FIGURE 2: Changes in pulmonary artery and aortic pressures following occlusion of the patent ductus by a balloon in Case No. 1.

cyanosis or squatting in early childhood. At age 15 she was examined in another hospital, and, a long, harsh systolic murmur was heard over the pulmonic area. The diagnosis of interventricular septal defect was then made. Restriction of activity was advised. Three years before admission to Chicago Wesley Memorial Hospital she had hemoptysis. She was markedly restricted in ability to perform ordinary daily physical activities. At the time of admission she was able to climb one flight of stairs with difficulty, and could walk only two blocks slowly without stopping.

She was well-developed, well-nourished and in no apparent distress at rest. There was definite cyanosis of her toenails and only slight bluish color of her fingernails. No clubbing was present. On physical examination there was a slight cardiac enlargement which was mainly right ventricular. There was a grade III blowing systolic murmur over the third interspace to the left of the sternum. No diastolic murmur could be heard. The pulmonary second sound was markedly accentuated. The x-ray film showed evidence of marked right ventricular hypertrophy and dilatation of the main stem pulmonary artery. The left ventricle, left atrium, and the right atrium were normal in size. There was increased pulmonary vascular marking. The electrocardiogram showed evidence of marked right ventricular hypertrophy and strain. Cardiac catheterization was performed and Table I gives the data obtained. The findings indicated a patent ductus arteriosus with partial reversal of the shunt. The calculated systemic arterial flow was significantly higher than the pulmonary artery flow. A successive angiocardiogram confirmed the diagnosis of patent ductus arteriosus without evidence of other anomalies.

She was then recatheterized and the ductus was occluded as described above. Figure 3 gives the pressures in the pulmonary artery and aorta following occlusion. There was no appreciable change in pressure up to five minutes after the occlusion of the

TABLE II

CHANGES IN PULMONARY ARTERY AND AORTIC PRESSURES AND O_2 SATURATION FOLLOWING OCCLUSION OF THE DUCTUS

		Case No. 1			Case No. 2		
Time	Location	Pressures mm Hg.	O_2 cont. Vol. Per Cent	Saturation Per Cent	Pressures mm Hg.	O_2 cont. Vol. Per Cent	Saturation Per Cent
Control	PA	110/60	9.8	54	112/65	17.2	66
	Aorta	115/70	13.3	72	105/65	21.0	81
1 min. after	PA	110/50	....	....	120/50	....	....
	Aorta	115/75	....	....	100/65	....	....
4 min.	PA	118/50	9.4	52	115/50	15.1	58
	Aorta	115/80	14.3	78	110/80	23.6	91
7 min.	PA	135/60	8.9	49	.....	....	....
	Aorta	120/85	14.4	78	.....	....	....
11 min.	PA	130/50	....	....	.....	....	....
	Aorta	120/90	....	....	.....	....	....
5 min. O_2 breathing	PA	120/40	....	....	110/60	....	....
	Aorta	120/85	17.6	96	.....	24.5	95
L ⟶ R shunt*		0.5 L/min.			1.3 L/min.		
R ⟶ L shunt		1.0 L/min.			1.3 L/min.		

*The shunts were calculated by the following formula:[8]

$$Sh_{L \longrightarrow R} = \frac{C_{PA\ \text{before occlusion}} - C_{PA\ \text{after occlusion}}}{C_{Aorta\ \text{after occlusion}} - C_{PA\ \text{before occlusion}}} \times \text{Effective pulmonary flow}$$

$$Sh_{R \longrightarrow L} = \frac{C_{Aorta\ \text{after occlusion}} - C_{Aorta\ \text{before occlusion}}}{C_{Aorta\ \text{before occlusion}} - C_{PA\ \text{after occlusion}}} \times \text{Effective pulmonary flow}$$

patent ductus. At that time the balloon was inadvertently pulled through the large ductus. Table II gives the changes in the saturation of the femoral and pulmonary arteries. The increase of the femoral artery oxygen saturation to the level of the right brachial artery saturation and the decrease of the pulmonary artery saturation indicate that the occlusion was approximately complete. From these figures, in contrast to the findings in Table I, only a slightly higher systemic flow than total pulmonary flow could be calculated, and it was assumed that the right to left shunt exceeded the left to right only slightly. Because there was no decrease in p ˡmonary artery pressure following occlusion of the ductus, and the existence of a ₖreater right to left shunt, it was decided not to surgically close the patent ductus.

Comment: These two cases illustrate the possibility of testing the response of the pulmonary artery pressure to occlusion of a patent ductus arteriosus without resorting to surgical exploration. In cases with pulmonary hypertension, all possible methods should be used prior to thoracotomy to arrive at the best prediction whether surgical closure will be beneficial or not. The described procedure is relatively simple, and it gives sufficient evidence to make the decision whether the patient is suitable for this operation. The dangers of the procedure seem to be minimal since it can be interrupted anytime. No complaints were expressed by our patients during occlusion and no disturbances in rhythm occurred.

In Case 1 the pulmonary artery pressure definitely increased after occlusion for four minutes and there was further increase after that. This indicates that the major shunt was right to left and the patent ductus served as an escape valve. The calculation of a larger pulmonary flow and of a greater left to right shunt using the oxygen saturation of the

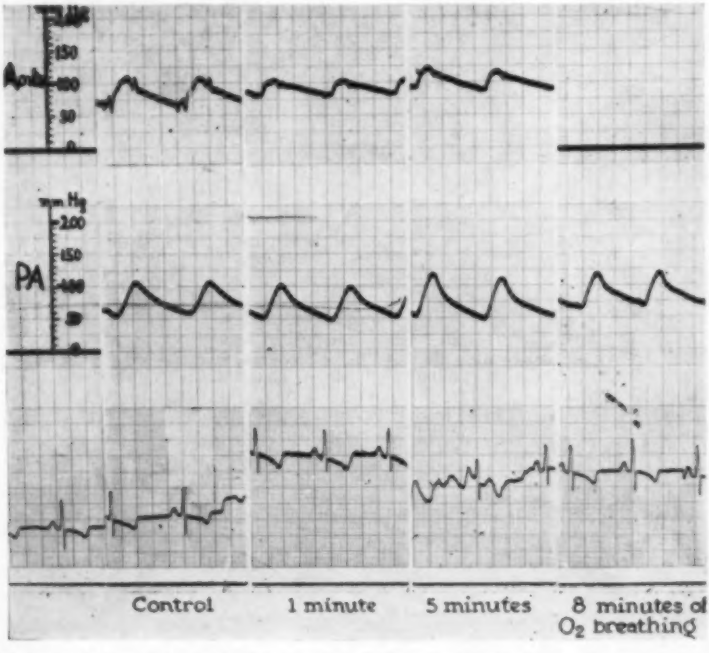


FIGURE 3: Changes in pulmonary and aortic pressures following occlusion of the patent ductus by a balloon in Case No. 2.

blood samples obtained during the first cardiac catheterization must, therefore, have been inaccurate. The changes in the oxygen saturation following occlusion of the patent ductus indicate that the major shunt was right to left in this case (Table II). In Case 2 a much higher systemic than pulmonary flow was calculated. However, the changes in saturation following obstruction of the ductus indicated that the systemic flow and thus the right to left shunt exceeded the pulmonary flow and the left to right shunt only slightly. The equal shunts explain the constance of the pulmonary and systemic pressure following occlusion in this case. It is evident that the calculation of shunts by the Fick principle cannot unrestrictedly be applied in the presence of bidirectional flow through the ductus, especially if the pulmonary venous return is desaturated because of impaired oxygenation in the lungs.

The lesson from the above findings and from the unfortunate outcome of the attempt to close the ductus in the first case is that the ductus should not be closed unless the pulmonary artery pressure decreases following preoperative obstruction, and unless the corrected shunt calculated from the changes following obstruction is mainly left to right. It was decided, therefore, not to attempt a closure in Case 2, despite the fact that the pulmonary artery pressure did not rise on obstruction.

SUMMARY

In patent ductus arteriosus with pulmonary hypertension and partial reversal of the shunt, the outcome of the surgical closure of the ductus depends on the direction of the major shunt and on the behavior of the pulmonary artery pressure following closure. Calculation of the shunts in the presence of bidirectional flow through the patent ductus is inaccurate using ordinary means. This report illustrates the possibility of prediction of the changes in pulmonary artery pressure and of a more accurate calculation of the shunts without surgical exploration. The ductus can be occluded during cardiac catheterization by a special three-way catheter with an inflatable balloon attachment which is placed into the patent ductus. The danger of the procedure does not exceed that of the usual cardiac catheterization and prevents the performance of an unnecessary thoracotomy.

RESUMEN

En le conducto arterioso persistente en hipertensión pulmonar y una inversión parcial del sentido en una intercomunicación (shunt) el resultado de la clausura quirúrgica del conducto depende la dirección del "shunt" mayor y de como se afecte la presión de la arteria pulmonar después del cierre. Por los medios ordinarios, la estimación de las intercomunicaciones en presencia de corriente bi-direccional es inexacta.

Esta comunicación ilustra la posibilidad de predecir los cambios en la presión de la arteria pulmonar y de valuar más exactamente las intercomunicaciones, sin exploración quirúrgica.

Los conductos pueden ser ocluídos durante la cateterización cardiaca por medio de un cateter de tres vías con una ampolla inflable que se coloca dentro del ductus persistente.

El peligro del procedimiento no es mayor que el de la cateterización habitual y evita el realizar una toracotomía innecesaria.

RESUME

Dans le cas de persistance du canal artériel de Botal avec hypertension pulmonaire et réversion partielle du shunt, le débit sanguin provenant de la fermeture chirurgicale de l'artère dépend de la direction du shunt principal et de l'état de la pression de l'artère pulmonaire après la fermeture. Le calcul des shunts en présence de débit à deux directions à travers le canal artériel ne peut être précisé si l'on utilise les moyens ordinaires. Cette communication démontre la possibilité de prévoir les altérations de la pression artérielle pulmonaire, et le calcul plus précis des shunts sans avoir besoin de recourir à l'exploration chirurgicale. L'artère peut être obstruée pendant une cathétérisation cardiaque au moyen d'un cathéter spécial à trois branches muni d'un ballonet gonflable qui est placé dans le canal artériel. Le risque du procédé n'excède pas celui de la cathétérisation cardiaque habituelle et évite l'utilisation d'une thoracotomie qui n'est pas indispensable.

ZUSAMMENFASSUNG

Bei offenen ductus arteriosus mit pulmonalem Hochdruck und partieller Umkehr des Kurzschlusses hängt das Ergebnis des chirurgischen Verschlusses des ductus ab von der Richtung des grösseren shunt's und dem Verhalten des pulmonalen Arteriendruckes nach dem Verschluss. Eine Abschätzung des shunt's bei Bestehen einer Strömung, die nach beiden Seiten durch den offenen ductus gerichtet ist, wird mit den gewöhnlichen Verfahren ungenau. Dieser Bericht veranschaulicht die Möglichkeit einer Vorhersage der Veränderungen im pulmonalen Arteriendruck und einer genaueren Abschätzung des shunt's ohne chirurgische Massnahme. Der ductus kann während einer Herz-Katheterisierung verschlossen werden durch einen speziellen Drei-Wege-Katheter mit einer aufblasbaren Balloneinrichtung, die in den offenen ductus eingeführt wird. Die Gefahr dieser Massnahme ist nicht grösser als die einer gewöhnlichen Herz-katheterisierung und verhindert die Vornahme einer nicht notwendigen Thorakotomie.

REFERENCES

1 Sones, F. M.: *Diagnosis and Treatment of Patent Ductus Arteriosus with Pulmonary Hypertension.* 28th Scientific Session of the American Heart Association, New Orleans, Oct. 22-24, 1955.

2 Rowe, G. G., et al.: *Surgical Closure of Patent Ductus Arteriosus Associated with Pulmonary Hypertension in Infants and Children.* 28th Scientific Session of the American Heart Association, New Orleans, Oct. 22-24, 1955.

3 Hultgren, H., Selzer, A., Purdy, A., Holman, E. and Gerbode, F.: "The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension," *Circulation*, 8:15, 1953.

4 Ellis, F. H., Jr., et al.: *Patent Ductus Arteriosus with Pulmonary Hypertension: An Analysis of Cases Treated Surgically.* American Association for Thoracic Surgery, Atlantic City, N. J., April 24-26, 1955.

5 London, F., Stevenson, T. D., Morran, A. G. and Haller, J. A.: *Patent Ductus Arteriosus with Reversal of Flow.* 28th Scientific Session of the American Heart Association, New Orleans, Oct. 22-24, 1955.

6 Brofman, B. L.: Personal communication.

7 Bothwell, T. H., et al.: "Patent Ductus Arteriosus with Partial Reversal of Shunt. A Study of Two Cases," *Am. Heart J.*, 44:360, 1952.

8 Cournand, A.: *Cardiac Catheterization in Congenital Heart Disease.* The Commonwealth Fund, New York, 1949.

Recent Experience in the Treatment of Silicotuberculosis

RAYMOND H. EVERS, M.D.
Plymouth, Wisconsin

Silicosis has long been a medical problem, and silicotuberculosis even more so. Prior to the advent of chemotherapy, treatment had been almost non-existent since the response to conventional methods was so poor. Isolation of the patient and symptomatic treatment were of some consolation but of little help. With the advent of the newer drugs for the treatment of tuberculosis of all forms, it was hoped that this problem was near a solution. The diagnosis as well as the treatment of silicotuberculosis pose difficult problems, which it is the purpose of this paper to discuss.

The prevalence of silicosis in the community represented by the writer is relatively high, because of the presence of industries in the area which in the past had atmospheres with high concentrations of silica dust. There are many cases of silicosis, especially among the older men in the community. Many of these have had years of exposure to silica during a time when the precautions now utilized for the protection of the workers had not been started. Since January 1, 1950, 88 patients with silicosis have been admitted to Rocky Knoll Sanatorium. Approximately 30 per cent of all men admitted are for evaluation or treatment of this disease when it is associated with tuberculosis.

Diagnostic Problems

During this period, and in the study of this group of patients, we have found many problems not common to the usual tuberculosis case.

1. The type of person involved frequently adds to the problem of early diagnosis. Most of them are older men, past the age of 60, who feel little urge to co-operate in the routine diagnostic x-ray film programs.

2. The symptoms of silicosis and silicotuberculosis are often misleading. The cough, wheeze, expectoration, dyspnea, vague chest pains, are common to both the complicated and uncomplicated silicotic. On this account, they are frequently ignored by both the patient and the doctor. In addition, many persons with both diseases develop severe psychic reactions to their diagnosis, since it has been common knowledge among laborers that the prognosis of this disease or combination of diseases, is poor. Accordingly, they choose to either ignore the recommendations of their medical advisers, or conversely, if only minimal silicosis is present, become overly anxious, often because of well-meant but over-exaggerated medical advice. Both reactions are understandable.

3. The interpretation of the chest x-ray film of the silicotic is notoriously difficult. With the superimposition of silicotic nodules and tuberculous infiltrations, it is impossible, even after long years of experience, to say with any degree of certainty, where one disease begins and the

other ends. In addition, the onset of both diseases is insidious. Frequently, five to 10 years of observation are necessary to determine any marked change. The mistake of comparing only the current film with the previous one is common. Even the granularity seen in early silicosis is difficult to differentiate from prominent lung markings of an elderly man. It has also been noticed by us that there is no way of predicting from the x-ray film appearance, that tubercle bacilli will be recovered. A fairly innocuous-looking x-ray film may be seen in a patient with positive cultures. Extensive soft densities may be present with areas suspicious of cavitation, and gastric cultures will be repeatedly negative.

4. Classification of silicosis into first, second, and third degree even creates problems for the clinician. This is determined by the size of the nodules and conglomerate masses which presents questions, since the size of the densities frequently varies with the type of film taken, the amount of exposure, etc. To be consistent, we shall avoid this classification.

5. To repeat a well-known fact in regard to this disease, negative laboratory examinations are always regarded with a grain of salt, even more than in the diagnosis of other diseases. It is often true that a clinician is forced to ignore a piece of negative laboratory evidence if it does not fit into the rest of a positive picture for diagnosis. In our early experience with silicosis, it happened frequently that a patient with much other evidence of clinical silicotuberculosis was denied treatment of his disease because tubercle bacilli could not be recovered from sputum, only to develop grossly positive sputum a few months later. For some reason as yet unexplained, tubercle bacilli are discharged from the lesion of this type of disease only infrequently.

Response to Treatment

When antimicrobial drugs first became available, patients were treated with one of the few drugs in existence, for relatively short periods of time. It eventually became obvious that long-term administration of combinations of drugs was mandatory to prevent recurrence. However, we are still undecided as to how long long-term therapy should be.

It was also noticed that the clinical response was poorer than in the average patient, especially if there was much dense fibrosis, with or without cavitation. The open cavitary healing noticed in other cases is less often seen in this group. This is another reason for emphasis on early diagnosis.

It has also been noted that relapse is more frequent in these patients than in our other groups of tuberculous patients. As an example, one has had two periods of hospitalization because he became positive after two years of streptomycin and para aminosalicylic and even though he had no evidence of cavitation, and was positive only on gastric cultures on his original admission.

Selection of Treatment Cases

Because of the difficulties, there has arisen the question of what cases of silicosis to treat for their complication of tuberculosis. Is it necessary to wait for the appearance of tubercle bacilli in sputum or gastric culture

before starting treatment? Because of the unreliability of these examinations, we think not. In addition to this, it is technically impossible to get cultures frequently enough on these vulnerable individuals to make them innocuous to their families and their community. Also, the type of person involved is frequently not of the mental status or of the age group to be completely cooperative. For the above reasons, we feel it advisable not to wait for the gross excretion of tubercle bacilli before offering the patient the benefits of antimicrobial therapy. In fact, waiting is often disastrous both to the patient and to his family.

We have set up the following criteria for determination of what cases to treat:

1. History of exposure to silica.
2. X-ray film suggestive of actual silicotuberculosis.
3. Serial x-ray film evidence of progression of disease.
4. Positive tuberculin test.
5. Other evidence of activity, such as hemoptysis, which is rare in uncomplicated silicosis, pleural effusion, or fever, elevated sedimentation rate, etc.

Such a course of selection of cases is not without error. There will be an occasional case which will be treated for silicotuberculosis, where x-ray film changes are due to progression of conglomerate silicosis. In our group, we have only one such case proved by autopsy. Perhaps there will be others proved at a later date. However, there is no evidence of damage to the patient by such treatment. Most such patients benefit by sanatorium care, their general condition improves, and we believe their lives are prolonged. In view of the potential danger of such individuals, both to themselves and to the community, we feel that this is a calculated risk which is well worth taking.

Case 1: J. G., an elderly retired man, born in 1880, first entered the sanatorium in October, 1950. He had been transferred from a general hospital where he was thought to have active silicotuberculosis. He had had extensive exposure to silica, working as a molder for 31 years, and in a pottery department for six years. His only complaint on admission was a vague feeling of pressure in the right lower chest. Physical examination revealed early senile changes, emphysema, coarse wheezing in the right mid-hemi-thorax. Tuberculin test was positive. Sputum and gastric cultures were negative for tubercle bacilli. X-ray film of the chest revealed bilateral nodularity scattered throughout both lung fields, with soft conglomerate densities in both upper lung areas. Because of the inability to recover tubercle bacilli, he was discharged after three months of observation, to be followed in the Out-Patient Department.

Following discharge, he was seen in clinic on May 19, 1951 when his x-ray film showed no change, and on November 24, 1951. On May 24, 1952, he was seen again, when his x-ray film showed evidence of cavitation in the left upper lung field. He was immediately admitted to the sanatorium, and his sputum was positive for tubercle bacilli on smear and culture. He was treated with PAS, 12 grams per day, and streptomycin, one gram semi-weekly, from the time of admission. On July 6, 1953, he was started on isoniazid, 100 mgm. t.i.d., in addition to the other drugs. At the start of each regimen of treatment, he showed symptomatic improvement, but x-ray films showed little change. He expired on April 19, 1955.

This case demonstrates graphically several points mentioned above. The laboratory gastric cultures were of little value in the early diagnosis of his tuberculous disease. The routine follow-up in the Out-Patient Department was likewise fruitless until he demonstrated a full-blown cavity. Lastly, it shows the poor response to chemotherapy of a case with cavitation. There

seems to be little inclination for cavity closure or open healing in the silicotic.

Case 2: G. L., an elderly white man, was referred to the Out-Patient Department in January, 1953, by an industrial physician because of suspicious x-ray findings. He was admitted to the sanatorium with a diagnosis of silicotuberculosis. There had been 36 years of exposure to silica in a cleaning room, foundry, and pottery. He complained of cough, expectoration, weight loss, and diffuse chest pain. Physical examination of the chest revealed only a few rales in the left apex after coughing. Sputum was positive for tubercle bacilli on smear and culture. X-ray films revealed evidence of bilateral nodular densities with superimposed soft conglomerate masses in the upper lung fields. Review of previous films taken at the factory revealed evidence of early silicosis in 1937. The conglomerate densities were first noted in 1949 and progressed steadily until the time of his admission in 1953.

He was treated with streptomycin, one gram per day for one month, followed by one gram semi-weekly. He was started on PAS, 12 grams per day, but developed severe nausea and vomiting, which necessitated discontinuance of the drug. He received isoniazid, 100 mgm. t.i.d., as a substitute. In August, 1953, laboratory studies showed resistance to both streptomycin and isoniazid. On this account, the former was discontinued. From this time on, he was uncooperative. He was tried on viomycin, terramycin, and again on PAS, but all were discontinued at his demand. His general condition deteriorated, and on January 21, 1955, he left the sanatorium against advice. He expired at his home on July 16, 1955.

This case was chosen for presentation because it reveals that the case of silicotuberculosis which progresses to the point where the disease is extensive and sputum is grossly positive, responds poorly, or not at all, to chemotherapy. This is not true for all cases, of course, but for a large percentage of ours.

Case 3: F. B., a white man, laborer, born in 1886, was first told that he had silicosis, complicated by tuberculosis, when he was admitted to a sanatorium in 1942. He had many years of exposure to silica-bearing dusts as a laborer in a local foundry. At the time of his first admission, he complained of cough, expectoration, chest pain, weight loss, fatigue, and dyspnea. Because of x-ray films evidence of soft exudative disease in the right upper lung field, superimposed upon early silicotic nodulation, sanatorium care was advised and accepted. He remained in the sanatorium from October 5, 1942 to December 15, 1945. X-ray films taken during this period showed evidence of cavitation with fluid level on one occasion. It was still impossible to recover tubercle bacilli. After he had received three years of bed rest, x-ray film showed some clearing of the softer elements of the disease. He was much improved symptomatically.

Subsequent follow-up in the Out-Patient Department revealed x-ray film evidence of early cavity emptying and filling. Tubercle bacilli could not be isolated, and thus he could not be hospitalized. In 1953, a routine tuberculin testing program in the community revealed positive tests in two of his grandchildren with whom he lived. After many months, he was persuaded to accept gastric cultures. These were negative for tubercle bacilli. He was then given sputum containers to send in specimens for culture once monthly. The first of these specimens was positive. He was admitted to the sanatorium for the third time on October 23, 1955. He was asymptomatic. Physical examination of the chest was within normal limits except for a few post-tussive rales in the right apex. He is being treated with isoniazid, 100 mgm. t.i.d., and sodium PAS, 12 grams per day.

This is a classic example of the difficulty of isolating tubercle bacilli from the silicotic with tuberculosis. It also shows the importance of tuberculin testing of contacts of the silicotic to demonstrate activity of his disease. Long before this patient demonstrated positive cultures, the tuberculin tests in his two grandchildren were positive. Also, this points out to us that, to prevent the dissemination of tubercle bacilli to these children, he should have been isolated long before he had a positive culture.

Case 4: B. S., an elderly white man, had 28 years of exposure to silica dusts while working as a bricklayer, using fire-brick, repairing the insides of boilers. In 1947, during a period of observation at Wisconsin General Hospital because of hoarseness, he was found to have silicosis. A sputum culture was positive for tubercle bacilli. Sanatorium care was advised but refused. In 1950, he was admitted to a local hospital, where his sputum was again found to contain tubercle bacilli. He now accepted sana-

torium care, and entered on March 15, 1950. Treatment consisted of streptomycin, one gram per day for 30 days, and Sodium PAS, 12 grams per day for three months. Sputum and gastric cultures became negative, but 10 months later became positive. He was given another three-month course of medication from July to October, 1951, and his sputum again converted to negative for one year. In July, 1952, he was started on isoniazid, 100 mgm. t.i.d. and streptomycin, one gram semi-weekly, and PAS, 12 grams per day. On August 1, 1953, he was discharged from the sanatorium, after 14 months of negative sputum cultures. Prior to his return to his daughter's home, she and her two children received BCG inoculation.

Three months after release, he was readmitted to the sanatorium for evaluation of his condition, because of symptoms of cough and expectoration. Numerous sputum cultures were negative for tubercle bacilli. After his symptoms had improved, he was returned to the home of his daughter in February, 1954. In May of that year, he was seen in the Out-Patient Department, where sputum was found to be positive for tubercle bacilli. He was immediately admitted for treatment. His daughter and her two children were observed closely because of contact. They developed no evidence of clinical tuberculosis, although their tuberculin tests changed from a mild BCG reaction to a highly positive reaction to first strength PPD. Several months later, a baby who lived in an apartment above the patient, developed tuberculous meningitis, with no other known contact.

On his third admission to the sanatorium, sensitivity studies performed on his tubercle bacilli showed no evidence of drug resistance. He was again treated with streptomycin and isoniazid in the usual dosage. His sputum became negative promptly but became positive eight months later. He expired from right heart failure on August 16, 1955.

This case demonstrates the futility of late diagnosis, the frequency of exacerbations, the unreliability of negative laboratory findings, the value of BCG vaccination of contacts, and again, the poor response to therapy. The baby who developed tuberculous meningitis subsequent to the exposure to the individual with silicotuberculosis, emphasizes the hazard of such a patient, even under frequent observation.

SUMMARY

1. During the past five years, 88 patients with silicotuberculosis were admitted to Rocky Knoll Sanatorium. Most of them were in the older age group and were foreign born.

2. Diagnosis of active tuberculosis in most of this group was difficult to establish because of perplexity in evaluating symptoms, atypical x-ray shadows of silicotuberculosis, and frequent inability to culture tubercle bacilli from excretions until excavation had occurred.

3. Poor response to chemotherapy and frequency of relapse was noted.

4. The following criteria are given to guide the physician in initiating chemotherapy in silicotuberculosis:

a. Positive tuberculin test. b. X-ray evidence suggestive of silicotuberculosis. c. Progression of conglomerate densities in series of films. d. Other evidence of activity: hemoptysis, fever, elevated sedimentation rate.

RESUMEN

1. Durante los últimos 5 años, 88 enfermos de silicosis se admitieron en el Sanatorio Rocky Knoll. La mayoría estaban en edades mayores y habían nacido en el extranjero.

2. El diagnóstico de la tuberculosis activa en la mayoría de este grupo fué difícil de establecer a causa de la perplejidad que producían los síntomas, manchas atípicas a los rayos X, de sicotuberculosis, y la frecuente imposibilidad de obtener bacilos por cultivo de las excreciones hasta que ocurría la excavación.

3. Se notó la deficiente respuesta a la quimioterapia y las recaídas frecuentes.

4. Se da el siguiente criterio para guiar al médico al iniciar la quimioterapia en la silicotuberculosis:

a. Reacción tuberculínica positiva. b. Evidencia radiológica sugestiva de silicotuberculosis. c. Aumento de las densidades confluentes en series de películas de rayos X. d. Otras evidencias de actividad: hemoptisis, fiebre, sedimentación acelerada.

RESUME

1. Pendant les cinq dernières années, 88 malades atteints de silico-tuberculose ont été admis au Sanatorium Rocky Knoll. La plupart d'entre eux étaient âgés et nés à l'étranger.

2. Chez la plupart de ces malades, le diagnostic de tuberculose active fut difficile à établir, à cause de l'absence de critère symptomatique indiscutable, les ombres radiologiques de silico-tuberculose n'ayant aucun caractère spécifique et les crachats ne contenant souvent pas de bacilles de Koch, tant que des cavités pulmonaires ne se soient pas constituées.

3. La chimiothérapie se montra peu efficace et les rechutes fréquentes.

4. Les auteurs se basent sur les critères suivants pour conseil ler le traitement chimiothérapique de la silico-tuberculose:

a. Test tuberculinique positif. b. Radiologie évocatrice de silico-tuberculose. c. Progression des confluences dans les films successifs. d. Autres symptômes d'activité: hémoptysie, fièvre, vitesse de sédimentation élevée.

ZUSAMMENFASSUNG

1. Während der letzten 5 Jahre wurde 88 Patienten mit Siliko-Tuberkulose in das Rocky Knoll Sanatorium eingewiesen. Die meisten von ihnen befanden sich in der älteren Altersgruppe und waren im Ausland geboren.

2. Die Diagnose einer aktiven Tuberkulose war vei den meisten Angehörigen dieser Gruppe schwer zu stellen wegen der Schwierigkeit in der Bewertung der Symptome, den atypischen röntgenologischen Veränderungen der Siliko-Tuberkulose und der häufigen Unmöglichkeit der Züchtung von Tuberkelbazillen aus dem Auswurf, ehe es zur Cavernenbildung kam.

3. Es wurde eine schlechte Reaktion auf die Chemo-Therapie und ein häufig Rückfall bemerkt.

4. Es werden die folgenden Kriterien aufgestellt zur Anweisung des Arztes bei der Einleitung einer Chemo-Therapie bei der Siliko-Tuberkulose:

a. Positiver Tuberkulin-Test. b. Röntgenologisch auf Siliko-Tuberkulose erdächtiger Befund. c. Zunahme von Konglomerat-förmigen Verdichtungen in röntgenologischen Verlaufsserien. d. Andere Zeichen von Aktivität als das sind Lungenblutungen, Fieber, erhöhte Blutsenkungen.

Roentgen Manifestations of Erythema Exudativum Multiforme (Stevens-Johnson Syndrome)

HARRISON SHAPIRO, M.D.* and ROBERT M. LOWMAN, M.D.
New Haven, Connecticut

Although the syndrome of erythema exudativum multiforme has been discussed in the general medial literature with particular emphasis on the dermatological and ophtha'mological aspects, little or no mention of it has been made in the American Radiological Literature. This is noted despite the fact that in many cases radiological consultation plays an important part in the management of the patients. The purpose of this paper, therefore, is to evaluate erythema exudativum multiforme with regard to its roentgen manifestations and to present two cases with characteristic roentgen findings.

Erythema exudativum multiforme was first described by Hebra[4] in 1866. It was regarded as an acute self-limited mild constitutional disease of unknown etiology characterized by varying types of mucocutaneous lesions. More severe expressions of this syndrome have subsequently been recognized, however, and labeled according to the site most severely involved, e. g. *eruptive fever with stomatitis and ophthalmia* (Stevens and Johnson)[10], *ectodermosis erosiva pluriorficialsis,* (Rendu)[7] *The mucosal respiratory syndrome,* (Stanyon and Warner),[9] and *dermatostomatitis,* (Baader)[2]. Reiter's disease is considered a related syndrome. Robinson and McCrumb[8] have grouped all of *these entities* together as *mucocutaneous ocular syndromes.* Most recently the Stevens-Johnson Syndrome has become the most popular name and is now almost synonymous with erythema exudativum multiforme.

The general clinical picture of erythema exudativum multiforme is usually characterized by a mild, self-limited acute afebrile illness with mucocutaneous involvement varying in degree from maculopapular to vesiculo-bullous. The most common sites of involvement are the skin, conjunctiva and the mucous membranes of the mouth, respiratory tract, genitalia, colon and rectum. This syndrome occurs at various ages but is seen most commonly in the second and third decades predominantly in males.

While no single specific etiological agent has been isolated, it is suspected that the disease is an allergic or hypersensitive reaction to various pharmacological and bacteriological excitants. Its occurrence has sometimes apparently been related to the administration of drugs such as aspirin, barbiturates, sulfonamides and phenolphthalein. Womack and Randall[11] feel that the herpes simplex virus may frequently be implicated and

From the Department of Radiology, Grace-New Haven Community Hospital, Yale University School of Medicine, Yale Medical Center.
*Presently at University Heights, Ohio.

in one case actually proved their contention with meticulous virologic and serologic determinations. Kove[5] reported this syndrome had occurred after the onset of mumps.

The laboratory findings are usually completely non-specific and are of value only in excluding other more specific entities. However, in two of Finland's[3] severe cases there was evidence suggesting a psittacosis-like virus. Furthermore, there are frequently high titers of cold agglutinins when pneumonia is present. Attempts to prove that the syndrome is due to the factors causing atypical pneumonia have not been convincing.

As yet no specific therapy has been propounded. Corticotropin and cortisone have been utilized with varying degrees of success. Mauriello[16] feels that in his experience these drugs have done little to alter the course of the disease. The treatment is symptomatic. Antibiotics have been used to prevent secondary infection particularly when the eyes are involved. Antihistamines may be of value and should be tried.

Fortunately the prognosis is good and the disease usually runs a self-limited course with complete regression of pathology. It is important to differentiate this syndrome from other diseases because of its benignity despite its occasionally severe appearance.

The chief roentgen manifestations are in the lung, where frequently pneumonitis occurs which is indistinguishable clinically, radiologically and often serologically from primary atypical pneumonia of unknown etiology. It is probably secondary to mucosal changes in the tracheobronchial tree

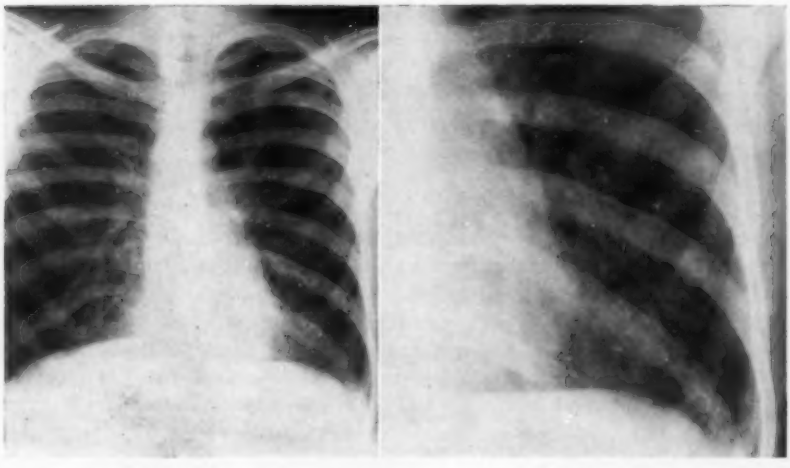


FIGURE 1A FIGURE 1B

Figure 1A: On the original film the small translucent areas thought to represent sites of bronchiolar emphysema were more marked. Streaked elongated area of infiltration with irregular nodular densities in the left lower lobe are shown. The densities persisted for 72 hours and following therapy a gradual resolution with disappearance of these densities was noted.—*Figure 1B:* Enlargement of the left lower lobe area demonstrating the character of the infiltrations.

which may vary in location, intensity, and time of onset as do the manifestations in other portions of the mucocutaneous system. Therefore, the roentgen appearance varies accordingly. In the mild cases the pneumonitis might be manifested only by a localized prominence of the bronchovascular markings, while in some of the fatal cases almost complete consolidation of both lungs has been noted. Thirty per cent of the cases of erythema exudativum multiforme described by Ashby and Lazar[1], approximately 20 per cent by Mauriello and 83 per cent of the cases described by Stanyon and Warner[9] had pneumonitis. The radiologist must be aware of the possibility of this development and should request progress films even if the initial chest film shows little or no evidence of pneumonitis.

Case 1: This 17 year old, white man, was admitted to the hospital complaining of fever, inflamed eyes, sore throat, dysuria, wheezing and an occasional cough, for eight days prior to admission.

He had a long allergic history with eczema and asthma since early childhood. During the two previous years at approximately the same time he had bouts of "virus pneumonia" accompanied by mouth lesions. Eight days prior to admission he became aware of a squeezing feeling in his chest at the end of inspiration, his appetite declined, he felt weak and dizzy and had an infrequent dry cough. He was diagnosed by his physician as having left lower lobe pneumonia and was given antibiotics. Shortly thereafter, his eyes became inflamed, the temperature rose to 103.5° F. and his mouth and throat became sore. Two days later he noted dysuria and was sent to the hospital for evaluation.

On physical examination he was well developed, well nourished but obviously in acute distress. The temperature was 104° F., pulse 110 and regular and respirations 24.

His lips were swollen and covered by a whitish crust. Maculopapular lesions on the dorsal and lateral aspects of the arms were noted. These varied from pin-point to 1 x 1 cm. in size. Some of these had pustular centers. A maculopapular rash on the penis with an erythematous area at the urethral orifice was noted. Vesicular lesions with erythematous margins were noted on the back.

The sclera were markedly inflamed with exudative material at the lid margins. The tongue and hard palate were coated. The uvula and buccal mucosa were inflamed.

Auscultation of the chest revealed coarse, generalized bronchial breathing with faint inspiratory and expiratory musical rales. The heart rate was rapid but otherwise unremarkable. At this time the clinical impression of Stevens-Johnson and/or Reiter's Syndrome was entertained.

Laboratory studies of smears from the mouth and penis for fungi were negative. The sputum smear revealed many gram positive cocci, some of which were diplococci some in chains. Blood cultures were negative. Sputum cultures showed normal flora. The tuberculin test was withheld. The cold agglutinins showed a trace at 1/80. The initial hemogram revealed 14.6 grams hemoglobin and white blood cell count of 6,400. The white count eventually progressed up to 15,150 but was down to 9,000 on discharge. Serological studies for psittacosis were non-reactive.

During the four days following hospital admission, his condition deteriorated. His respirations were sonorous and rattling. The fever varied from 99.6° F. to 104.4° F. and the erythema gradually became more prominent. Treatment consisted of generalized supportive measures and systemic administration of cortef and cortisone.

Five days after admission the fever began to subside and the skin lesions were starting to dry up. However, the chest symptoms persisted and eight days after admission a definite area of infiltration in the left lower lobe was noted. Previously radiographic evidence of pneumonitis was not present. At this time the white count had risen and positive cultures were obtained from the eyes, therefore, he was placed on streptomycin and procaine penicillin. From then on gradual improvement was noted. Cortisone was gradually reduced and on the 18th hospital day he was discharged following almost complete resolution of the disease process.

Case 2: This three year old white girl was well until one week prior to admission when a small raised, slightly red area above the left brow was noted. The child was asymptomatic and afebrile at this time. Three days prior to admission lesions were found on the forearms, thighs, and were particularly prominent along scratch marks thought to be inflicted by the household cat. Her physician started sulfa drugs which

were continued until the day of admission. The lesions continued to spread and became pruritic. The day prior to admission she complained of pain in the calves and refused to walk. The day of admission her temperature was 102° F.

Her past history was non-contributory, however, a 10 year old sister had an asthmatic history and a strong history of eczema was present in her mother's family.

She was a well developed, alert, well nourished girl not appearing acutely ill. However, her temperature was 101° F., pulse 160 and respirations 28.

Rashes were present consisting of isolated and confluent lesions which were round, raised, circumscribed and had umbilicated areas. Some were crusted. Their peripheries were erythematous, indurated and scaly. Confluent areas were seen on the brows, circumorally and on the right thigh and both calves. Isolated lesions were noted on the trunk, back, neck and arms. No lesion was noted on the scalp.

The tonsils were slightly enlarged. Two large nodes were palpable in each axillar and shotty nodes were present in both inguinal regions.

The lungs and heart were unremarkable. The remainder of the physical examination was negative.

Laboratory studies included a normal EKG, negative urinalysis, elevated white blood cell count with shift to the left and no eosinophilia. Nose and throat cultures grew out pneumococci.

Five days after admission she developed conjunctivitis, mouth lesions, spiking fever, and progression of the rash, especially in the areas of the back and buttocks. It was thought that she might have Stevens-Johnson syndrome. Because she did not improve on symptomatic treatment she was started on cortisone, 200 mg. daily. The rash then improved markedly and she became more comfortable. However, eight days after admission she developed signs of pneumonia and a chest x-ray film revealed infiltration in the lower lobe of the right lung. Terramycin was begun and a gradual clearing of the pneumonitis occurred. Cortisone was discontinued at this time. However, following the recession of the pneumonitis, a recurrence of the skin rash occurred. This was quickly brought under control with benadryl and she was discharged, markedly improved 30 days after admission.

It is interesting to note that both patients present strong allergic backgrounds. The onset of the syndrome was heralded by broncho-pulmonary symptoms in Case 1, while in Case 2 no evidence of pneumonitis was noted

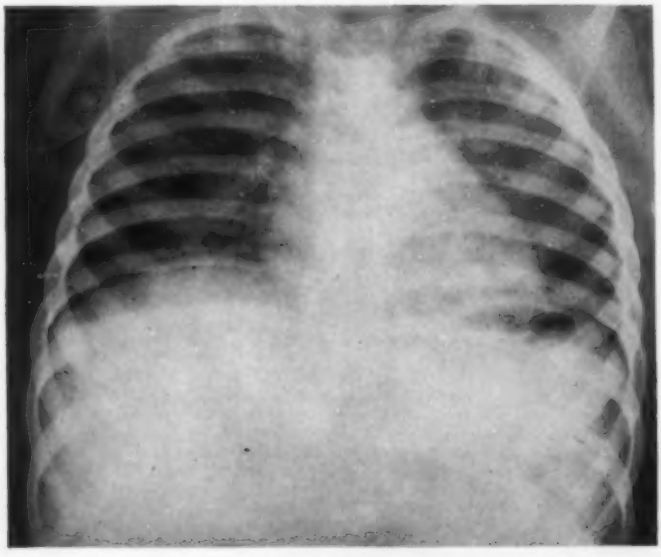


FIGURE 2: An atypical right cardiophrenic infiltration is shown.

until the peripheral mucocutaneous and occular findings were well established. The pneumonitis of the former was much more severe than that of the latter. Many of the cases reported by Stanyon and Warner were comparable in severity to our first case. The second case, however, was characterized on admission only by slight fever and mild rash. Despite the development of pneumonitis this child was never as severely ill as the first. Since the degree of involvement may be so variable it is possible that many mild cases of pneumonitis in conjunction with erythema exudativum multiforme may be overlooked.

Although pneumonitis is not always present, its occurrence should be anticipated so that the patient may have the benefit of alert supportive management. Despite the usually favorable ultimate prognosis, the patient may be so ill that not infrequently during the height of the illness the physician might have just cause to doubt eventual recovery. Three deaths have been reported by Finland and two by Stanyon and Warner in this syndrome. The potential severity of erythema exudativum multiforme cannot therefore, be underestimated.

SUMMARY

1. Erythema exudativum multiforme is usually an acute, mild exanthematous disease of little apparent consequence.

2. Syndrome may appear in severe forms manifested by bulbous erythematous lesions involving the mucocutaneous areas of the body.

3. The mucosa of the respiratory tract may be involved producing pneumonitis which is radiographically, serologically and clinically indistinguishable from primary atypical pneumonia.

RESUMEN

1. El eritema exudativo multiforme habitualmente es una enfermedad moderada, exantematosa de aparentes pocas consecuencias.

2. El síndrome puede aparecer en formas severas manifestándose por lesiones vesiculosas eritematosas invadiendo las áreas muco-cutáneas del cuerpo.

3. La mucosa de las vías respiratorias puede ser afectada produciendo neumonitis que no puede distinguirse radiológicamente, ni clínica o serológicamente de la neumonía primaria atípica.

RESUME

1. L'érythème exsudatif multiforme est habituellement une affection éruptive, aiguë, de moyenne intensité, et qui a peu de conséquences apparentes.

2. Dans les formes sévères, le syndrome peut se présenter avec des lésions érythémato-bulleuses atteignant la peau et les muqueuses.

3. Les muqueuses de l'arbre respiratoire peuvent être atteintes, et il en résulte une pneumopathie qui radiologiquement, sérologiquement et cliniquement, ne peut être distinguée de la pneumonie primaire atypique.

ZUSAMMENFASSUNG

1. Erythema exsudativum multiforme ist für gewöhnlich eine akute, milde, exanthematöse Erkrankung mit wenig zutage liegenden Folgen.

2. Syndrome können in Erscheinung treten bei schweren Formen, die zur Darstellung kommen als bullöse erythematöse Herde, wobei alle Schleimhautbereiche des Körpers beteiligt sind.

3. Die Mucosa des Respirationstraktes kann beteiligt sein und zu einer Pneumonitis führen, die von einer primär-atypischen Pneumonie röntgenologisch, serologisch und klinisch nicht zu unterscheiden ist.

REFERENCES

1 Ashby, D. W. and Lazar, T.: "Erythema Multiforme Exudativum Major (Stevens-Johnson Syndrome)," *Lancet*, 1:1091, 1951.

2 Baader, E.: "Dermatostomatitis," *Arch. Dermat. Syph.*, 149:261, 1925.

3 Finland, M., Jolliffe, L. S. and Parker, F., Jr.: "Pneumonia and Erythema Multiforme Exudativum," *Am. J. Med.*, 4:473, 1948.

4 Hebra, F.: *On Diseases of the Skin, Including the Exanthemata*, Vol. I, p. 285, London, 1866. The New Sydenham Soc.

5 Kove, S.: "Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis)," *Am. J. M. Sc.*, 210:611, 1945.

6 Mauriello, D. A.: "Erythema Multiforme Exudativum (Stevens-Johnson Syndrome)," *J.A.M.A.*, 156:1495, 1954.

7 Rendu, R.: "Sur un syndrome characterise par l'inflammation simultanee de toutes les muqueuses externes (conjunctivale, nasale, linguale, buccopharyngee, anale et balano-preputiale) coexistant avec une eruption varicelliforme puis purpurique des quatre membres," *Rev. gen. de clin. et de therap.*, 30:351, 1916.

8 Robinson, H. M., Jr. and McCrumb, F. R., Jr.: "Comparative Analysis of the Mucocutaneous-ocular Syndromes, Report of Eleven Cases and Review of the Literature," *Arch. Dermat. Syph.*, 61:539, 1950.

9 Stanyon, J. H. and Warner, W. P.: "Mucosal Respiratory Syndrome," *Canad. M. A. J.*, 53:427, 1945.

10 Stevens, A. M. and Johnson, F. C.: "A New Eruptive Fever Associated with Stomatitis and Ophthalmia. Report of Two Cases in Children," *Am. J. Dis. Child.*, 24:526, 1922.

11 Womack, C. R. and Randall, C. C.: "Erythema Exudativum Multiforme," *Am. J. Med.*, 15:633, 1953.

Case Report Section

A Case of Polyarteritis Nodosa with Multiple Infarcts in the Lungs

S. SOCHOCKY, M.D.
Cambridge, England

Polyarteritis nodosa is associated with a wide range of clinical manifestations including fever, anaemia, progressive asthenia, leukocytosis, accelerated erythrocyte sedimentation rate, and local symptoms due to scattered arterial lesions. Almost every part of the body is affected during the course of the disease. Mourey and Hundberg point out that polyarteritis nodosa may simulate such conditions as enteric fever, septicaemia, tuberculosis, dysentery, acute nephritis and others. The nervous system, skin and kidneys are affected in a relatively large percentage of described cases. According to Harriman, changes in the lungs are present in 20 to 40 per cent of cases. X-ray films of the chest show patchy infiltration, round lesions in the lungs, or pleurisy with or without effusion. The case reported below is of interest because the main symptoms were related to the lungs from the onset of the illness.

Case Report: A man aged 51 years was admitted to this hospital for investigation with a presumed diagnosis of either malignancy of multiple abscesses.

The family history was negative. He had appendicitis, jaundice in 1936, pneumonia in 1939, malaria and sandfly fever during World War II.

He had had recurrent pneumonic infection since early July 1955, which had not completely resolved. He was at first treated at home with antibiotics but, was admitted to the hospital July 26, 1955, when there was recrudescence of cough and fever, as well as pleuritic pain in the right base. He was kept on antibiotics but improvement was slow. X-ray film taken August 9, 1955 showed rounded opacities in the right upper and mid zones and left upper zone with fluid in the left base (Fig. 1). Treatment with antibiotics was continued but there was no improvement. X-ray film taken August 20, 1955 showed rounded opacities scattered throughout the right lung and in the left upper zone with fluid at the right base (Fig. 2). Culture of aspirated fluid was reported as sterile.

On admission, September 3, 1955, he was an ill-looking man, febrile, anaemic and dyspnoeic. He complained of pain in the left lower chest, had dry cough. His appetite was poor and he was losing weight.

Clinical examination revealed no abnormality except crepitations over base of each lung, tenderness over epigastrium and liver extending three finger breadths below the costal margin.

Laboratory investigations revealed the following abnormal conditions: Red blood cells—3.2 million; haemoglobin 69 per cent; colour index 1.08; white blood cell count—16,900; neutrophils 70; stab 7; juveniles 0; myelocytes 0; lymphocytes 9; monocytes 6; eosinophils 7; basophils 0; slight macrocytosis; erythrocyte sedimentation rate 56mm./1 hour Westergren.

Sternal marrow biopsy revealed marked myeloid hyperplasia with plasma cell increase.

Stools were strongly positive for occult blood.

Urine: specific gravity 1,006; albumin 90 mg. per cent; leukocytes numerous; red blood cells moderate; casts, coarse granular, very numerous; culture, moderate growth of coagulase positive *Staph. aureus* obtained.

Chest x-ray films showed circumscribed lesions at anterior end of fourth right rib and small rounded opacity at anterior end of left second rib. There was also a small collection of fluid in the left costo-phrenic angle, and the right costo-phrenic angle was obscure.

Bronchoscopy did not reveal any abnormality. Muscle biopsy was not done.

His general condition rapidly deteriorated. The blood picture 11 days after admission showed haemoglobin 67 per cent; red blood cells 2.9 million; white blood cell count 36,500; neutrophils 76; stab 10; leukocytes 10; monocytes 3; eosinophils 1; blood

urea rose to 210 mg. per cent in the same period. Pleural aspirates remained sterile.

Chest x-ray films taken September 16, 1955 showed the rounded clearly defined opacities, present in the previous film. There was bilateral pleural effusion.

While in hospital he had only symptomatic treatment. He died 19 days after admission.

Macroscopic findings: Firm, well defined greyish-white to creamy-yellow ovoid or spherical nodules (0.3 by 0.3 by 0.2 cm. up to 2.5 by 3 by 1.8 cm.) with rather opaque cut surfaces were present in all lobes of both lungs. There were between four (right middle lobe) and 11 (left upper lobe) nodules in each lobe, usually situated immediately beneath the visceral pleura and widely scattered except in the left upper lobe where several large nodules were clustered together along the anterior border. At the apex of each upper lobe there was a firm plaque (right: 6 by 3.8 by 2 cm.; left: 3.4 by 3.2 by up to 1.8 cm.) consisting of opaque yellowish-white caseous material. Apart from these nodules and plaques the lung tissue was moderately congested towards the hilum but otherwise appeared normal. Moderate amounts of slightly cloudy amber-coloured fluid with flakes of fibrin in both pleural cavities (right: 320 millilitres approximately, left: 400 millilitres approximately).

The "creamy-yellow ovoid or spherical nodules" consisted of necrotic eosinophilic material surrounded by granulation tissue and denser fibrous connective tissue and were probably partially organised infarcts (Figure 3). The architecture of blood vessels and other structures can still be discerned in the eosinophilic material which also contained a few necrotic multinucleate giant cells and abundant nuclear debris. No bacteria or fungi were discovered in Gram, Ziehl-Neelsen or periodic-acid-Schiff preparations. A partially organised fibrinous exudate was present on the pleural surface over the nodules and to a lesser extent elsewhere. The alveolar walls in the lung tissue around the infarcts were often thickened by fibrous connective tissue. There were scattered areas of bronchopneu-

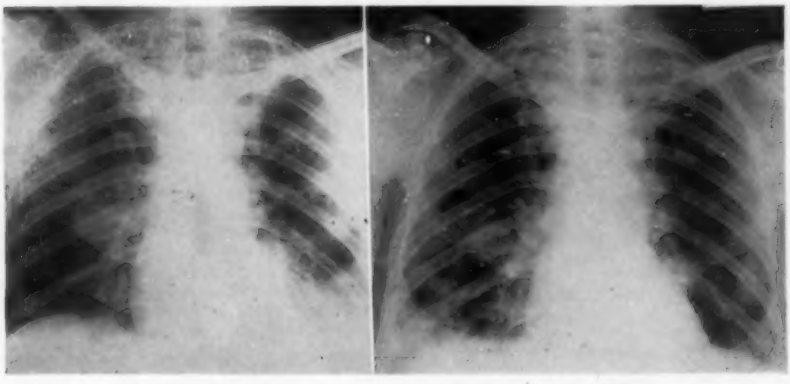


FIGURE 1 FIGURE 2

Figure 1: X-ray film of chest taken August 9, 1955 shows rounded opacities in both upper and mid zones of both lungs with fluid in the left base.—*Figure 2:* X-ray film taken August 20, 1955 shows rounded opacities seen in film taken on August 9, 1955 still present; clear costophrenic angle but with pleural fluid in the right base.

monia throughout the lungs.

Infarcts were also found in the myocardium, kidneys (Figure 4), suprarenals, spleen and testes.

REFERENCES

1 Ralston, D. E. and Krale, W. F.: "The Renal Lesions of Periarteritis Nodosa," *Proc. Mayo Clin.*, 24:18, 1949.
2 Wold, L. E. and Baggenstos, A. H.: "Gastro-Intestinal Lesions of Periarteritis Nodosa," *Proc. Mayo Clin.*, 24:28, 1949.
3 Sweeney, A. R. and Baggenstoss, A. H.: "Pulmonary Lesions of Periarteritis Nodosa," *Proc. Mayo Clin.*, 24:35, 1949.
4 Parker, H. L. and Kernohan, J. W.: "The Central Nervous System in Periarteritis Nodosa," *Proc. Mayo Clin.*, 24:43, 1949.
5 Lovshin, L. L. and Kernohan, J. W.: "Peripheral Neuritis in Periarteritis Nodosa," *Proc. Mayo Clin.*, 24:48, 1949.

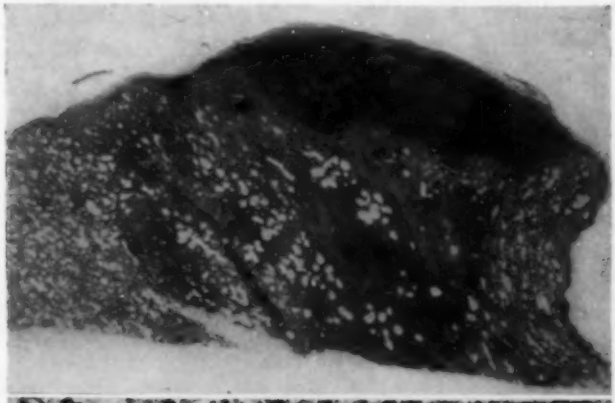


FIGURE 3

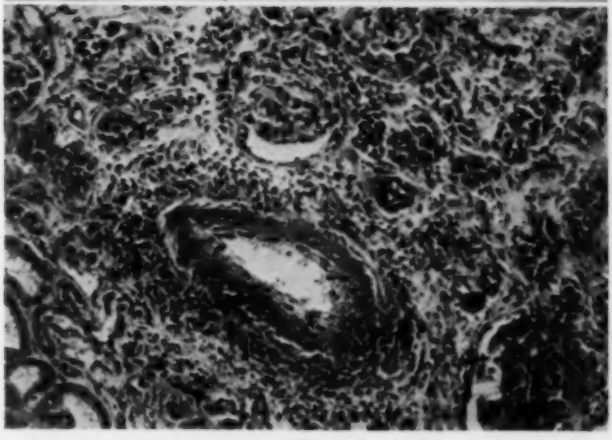


FIGURE 4

Figure 3: Low-power view of a pulmonary infarct (x 2.5). The infarct is the sharply defined dark, sub-pleural area. It is covered by thickened pleura, has a necrotic centre and on its pulmonary aspect a zone of polymorphonuclear infiltration. The underlying lung features patchy pneumonia and oedema. (H and E stain.)—*Figure 4:* High power view (x 130) of an acute disorganisation of a renal arteriole by fibrinoid necrosis and polymorphonuclear invasion of its wall; similar changes are present in other vessels of the same section. The capillary tufts of many glomeruli are also involved, see for example in corner of photograph. (H and E stain.)

6 Summers, V. K.: "The Nervous Manifestations of Periarteritis Nodosa," *Lancet*, 1:1148, 1950.
7 Winkelman, N. W. and Moore, M. T.: "Disseminated Necrotizing Panarteritis (Periarteritis Nodosa): A Clinico-Pathologic Report," *J. Neuropath. exp. Neurol.*, 9:60. 1950.
8 Mackay, M. E., McLardy, T. and Harris, C.: "A Case of Periarteritis Nodosa of the Central Nervous System," *J. ment. Sci.*, 96:470, 1950.
9 Churg, J. and Strauss, L.: "Allergic Granulomatosis, Allergic Vigitis and Periarteritis Nodosa," *Am. J. Path.*, 27:277, 1951.
10 Wilens, S. L. and Glynn, J.: "Hypertensive and Nonhypertensive Periarteritis Nodosa," *Arch. Int. Med.*, 88:51, 1951.
11 Stratton, H. J. M. et al.: "Granuloma of the Nose and Periarteritis Nodosa," *B.M.J.*, 1:127, 1953.
12 Leading Article: "Periarteritis Nodosa," *Lancet*, 11:693, 1954.
13 Harrison, T. R.: "Principles of Internal Medicine."
14 Darmady, E. M.: "Renal Tubular Failure Associated with Periarteritis Nodosa," *Lancet*, 1:378, 1955.

Bronchogenic Leiomyosarcoma

Case Report with Necropsy Findings

HARRY G. HICKS, M.D.*
Long Beach, California

Leiomyosarcomas generally arise from smooth muscle of the uterus or gastrointestinal tract. Intrapulmonary tumors of smooth muscle origin are rare. There have been few case reports in the past of sarcomas arising from the bronchus,[1, 2, 3, 4] but cases of leiomyosarcoma are even more infrequent.[5, 6, 7, 8] In a recent article,[9] four cases were presented with clinical data and pathologic findings. Most of the cases reported have been based upon conclusions reached from examination of surgical specimens. Case reports based upon complete necropsies are infrequent.

Case Report

A. H., a 79 year old white man was admitted to the Long Beach Veteran's Administration Hospital with a three day history of sudden onset of dyspnea associated with cough, productive of frothy white sputum and some pink streaking. For the past two months he had a cough with mucoid sputum and occasional blood streaking. In the past he was hospitalized at another institution for repair of a right inguinal hernia.

Physical Examination: Temperature 99° F., pulse 130, blood pressure 186/92. On admission there was cyanosis with distention of cervical veins. Breath sounds were diminished over both lung fields and dullness over the right upper anterior chest was present. Cardiomegaly with three plus pitting edema of the extremities was demonstrated.

Laboratory: White blood cell count 10,200; erythrocyte sedimentation rate 37 mm./hr. X-ray film of the chest (Figure 1) revealed generalized patchy infiltrate throughout both lung fields with a dense 9 x 10 cm. opacity in the region of the right hilum. Also, cardiac enlargement was demonstrated. Emergency measures for pulmonary edema consisted of oxygen under pressure, bed rest, fluids and digitalization with digoxin, aminophyllin suppositories, mercurial diuretics, and sodium phenobarbital. Penicillin and streptomycin were also started. Clinical improvement was prompt with relief of cyanosis and dyspnea. The clinical impressions were bronchogenic carcinoma and hypertensive cardiovascular disease. A second episode of pulmonary edema occurred that was controlled with morphine, atropine, aminophyllin and positive pressure oxygen. He continued to deteriorate and expired 16 days after admission to the hospital.

At necropsy: The right pulmonary apex was firmly adherent to the chest wall superiorly, laterally and posteriorly. The right lung weighed 1500; the left 950 grams. At the orifice of the right upper lobe bronchus, approximately 2 cm. from its origin, there was obstruction and replacement of the bronchus and adjacent pulmonary tissue

*Veteran's Administration Hospital, Department of Laboratories. Presently in Ogden, Utah.

by a tumor which measured 10 cm. in diameter. It was partially necrotic, whitish and fleshy. The pulmonary parenchyma of both the right and left lung was diffusely involved with circumscribed, whitish tumor nodules. There were similar nodules located subpleurally. The lymph nodes in the pulmonary hilar region were grossly replaced by neoplastic tissue similar to that observed in the lungs.

In the parenchyma of the right lobe of the liver there was a 1 cm. well circumscribed

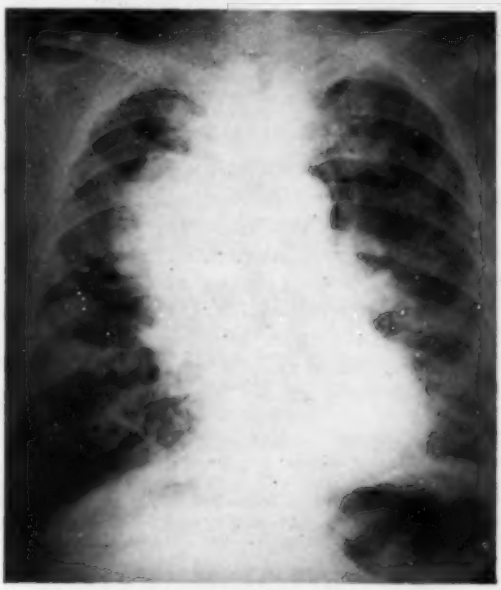


FIGURE 1: Posterior-anterior projection of chest at time of admission.

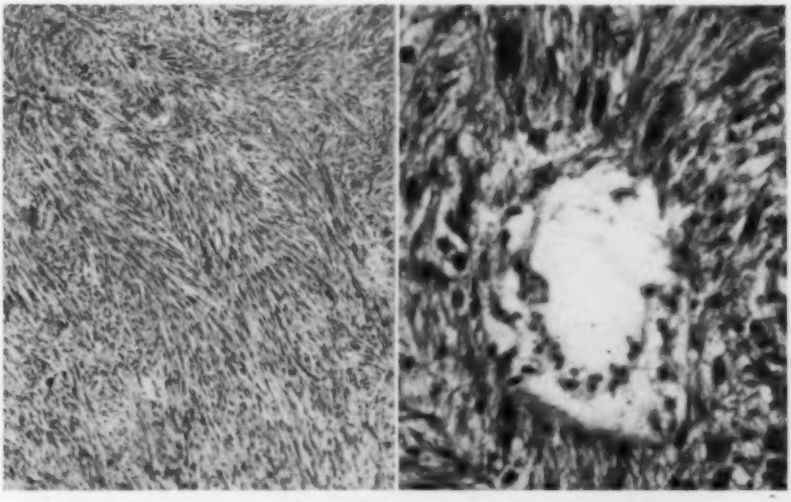


FIGURE 2A FIGURE 2B

Figure 2A: Low power view of the tumor (H & E stain, 100X).—*Figure 2B:* High power view of tumor which has destroyed blood vessel wall (H & E stain, 700X).

nodule of tumor tissue which grossly compressed the adjacent normal appearing liver substance.

Gross Pathological Diagnoses: 1. Bronchogenic carcinoma, right upper lobe bronchus with metastases to both lungs, hilar lymph nodes, and nodule in the liver. 2. Generalized arteriosclerosis. 3. Arteriolar sclerosis, kidneys. 4. Nodular hyperplasia, prostate. 5. Cholelithiasis.

With hematoxylin and eosin stain (Figure 2), the tumor in most areas consisted of interlacing bands of spindle cells with elongated blunted nuclei, and an occasional area of palisading. However, some of the cells suggested a pleomorphic cell carcinoma. The Masson's trichrome and van Gieson's stains revealed little collagen, and the cells were staining in conformity with muscle cell origin. Many sections were studied after phosphotungstic acid hematoxylin stains, and showed absence of striations in the spindle shaped cells.

Microscopic Diagnosis: Myosarcoma (probable leiomyosarcoma), right upper lobe bronchus.

DISCUSSION

The rarity of intrapulmonary leiomyosarcomas is evidenced by only 10 being reported in the period 1938-1954. The youngest was a four year old boy, the oldest a 67 year old woman. The tumor has been found to be more frequent in males, 9:4. Location of these intrabronchial tumors were as follows: right upper lobe four; right middle lobe two; right main stem bronchus one; left upper lobe two; left lower lobe three; left main stem bronchus one. Three cases were autopsied. In two the tumor was confined to the thoracic cavity while the other had widespread metastases.

Acknowledgments: The author wishes to acknowledge the professional aid of B. E. Konwaler, M.D., Chief of Laboratories, Veteran's Administration Hospital, Long Beach, California. Mrs. Ann Shell and Mrs. Gladys Wikstrom gave secretarial assistance in the preparation of the manuscript. The photography was done by the Medical Photography Department, Veteran's Administration Hospital, Long Beach, California.

REFERENCES

1 Pollock, B. S., Cohen, S., Borrone, M. and Grossi, A. M.: "Primary Sarcoma of Bronchus: Case Report," *Am. J. Roentgen.*, 41:909, 1939.
2 Lewis, I.: "Sarcoma of Bronchus," *Proc. Roy. Soc. Med.*, 40:119, 1947.
3 Baum, O. S., Richard, J. H. and Ryan, M. D.: "Case of Atelectasis of Right Lower and Middle Lobes with Bronchoscopy Demonstrating Spindle Cell Sarcoma of Right Main Stem Bronchus," *Ann. Int. Med.*, 12:699, 1938.
4 Baum, O. S., Silverman, G., Rash, R. and Riley, R. L.: "Case of Spindle Cell Sarcoma of Bronchus; Supplementary Report," *Ann. Int. Med.*, 17:750, 1942.
5 Neumann, R.: "Leiomyosarkom der Lunge," *Ztschr. f. Path.*, 52:576, 1938.
6 Randall, W. S. and Blades, B.: "Primary Bronchogenic Leiomyosarcoma," *Arch. Path.*, 42:543, 1946.
7 Johnson, G. K., Mongiardi, J. L. and Jacobs, J. B.: "Primary Leiomyosarcoma of the Lung Treated by Pneumonectomy," *Surgery*, 32:1010, 1952.
8 Brunn, H. and Goldman, A.: "The Differentiation of Benign from Malignant Polypoid Bronchial Tumors," *Surg. Gynec. and Obst.*, 71:703, 1940.
9 Watson, W. L. and Anlyan, A. J.: "Primary Leiomyosarcoma of the Lung," *Cancer*, 7:250, 1954.

Malignant Mesothelioma of the Pleura

ARMANDO TRAMUJAS, M.D.,* and GIOCONDO VILLANOVA ARTIGAS, M.D.**
Curitiba, Brazil

This tumor was described by Wagner in 1870. Biggs reported the first case in North American literature. In general there is agreement

*Pathologist, Curitiba, Brazil.
**Surgeon, Curitiba, Brazil.
Presented before the "Terceiro Congresso Brasileiro de Doenças do Torax." Fortaleza, Brasil, December 5-10, 1955.

that pleural mesotheliomas are primary tumors. However, Willis, Gunn, Friedmann and others, believe such blastomas are always spread from bronchial carcinomas or similar tumors situated in non pulmonary areas. The majority of pathologists now think this tumor is a clinical and pathological entity.

In 1942, Stout and Murray reported on this subject and their account is a landmark in the history of this tumor. From that time, diagnostic errors became less frequent, and at the same time the tumor also became more rare in medical literature.

Until 1944, Hochberg reported 36 cases taken from the world literature. Hertzog had a case in 1945, of a man 60 years old, who died within eight months, of the beginning of symptoms. In 1946, Weissmann reported two new cases, one of them with necroscopic verification. The same year, Piatt reported a fatal case, in a woman 33 years old, with a two year evolution of the tumor.

In 1950, Whitehead, reported a fatal case of a man that, presenting cough, dyspnea and thoracic pain, died 14 days after his admission to the hospital. At necropsy, he presented a general thickened pleura, rich in mucous substance and a collapsed but not invaded lung. In that same year, Campbell reported four new necropsied cases. In 1951, Hochberg reported 7 cases taken from various New York hospitals, four of them being localized forms, surgically treated.

Dell'Acqua, in 1951, had a case with the characteristics of a spreading tumor, ended by death. The same happened to a case of Adorni and Coles from Buenos Aires, also in 1951.

Benoit and Ackermann presented six new cases of localized mesotheliomas, in 1953, three of them with malignant characteristics. Yesner and Urwitz, in 1953, reported a case of a localized and well circumscribed mesothelioma, essentially epithelial, that is a characteristic of malignancy.

Lindskog and Liebow reported, another case of a diffuze mesothelioma of the pleura, in 1953, in a man 40 years old. Submitted to a pleuropneumonectomy, the patient died soon after the operation, by pulmonary

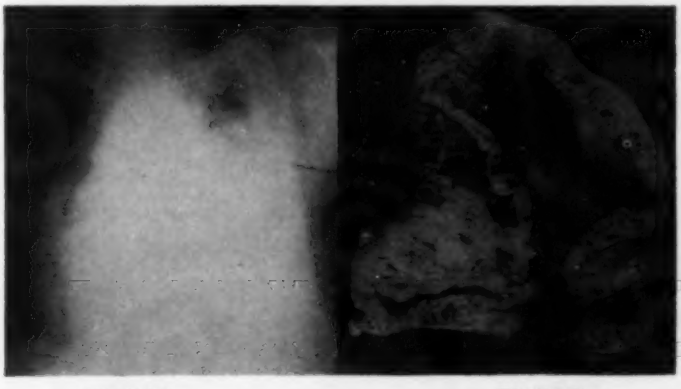


FIGURE 1

FIGURE 2

oedema caused by blood transfusion accident. The surgical specimen showed thickened pleura that was irregular soft and translucid, or solid. The bronchuses has been opened and bronchial carcinoma was not found. Microscopically, the tumor had various forms in the different points examined: papillary like structures, or with the arrangement of adenocarcinoma and irregular groups of neoplastic cells.

In Brazilian literature there is one case of malignant diffuse mesothelioma, in an 8 year old child, reported by Tavares de Lima et al, in 1953.

In 1954, Jenny and Ulsperger, made a revision over 16 mesotheliomas, eleven of which originated on the pleura. All of them had been fatal and verified at necropsy.

Bogardus et al, presented four new cases of pleural mesotheliomas, in 1955, but only one with the characteristics of diffuse malignant tumor.

In this report we are presenting the second Brazilian case of diffuse malignant mesothelioma of the pleura and the first world case of a tumor like that surgically treated with temporary success.

Case Report: A white man, 47 years old, well nourished, had pain in the left hemithorax for five months, cough, and weight loss (4 kilograms). Examination revealed clubbing of fingers, du.lness of the left hemithorax and absence of breath sounds on this side. An x-ray film showed diffuze opacity of the left hemithorax, more evident at the base (Fig. 1). The endoscopist saw evidence of passive congestion of the left main bronchus, with partial extrinsic obstruction of the lower lote branch. No fluid was obtained by pleural puncture.

Laboratory findings were non-contributing.

On January 5, 1954 thoracotomy revealed dense adhesions, with suggestive calcification, between the visceral and parietal layers. Extrapleural digital blunt dissection was performed over the surface of the mass. In the hilum, there were no adhesions or enlarged nodes.

The tumor was removed and macroscopically the lung presented a deformed superficial appearence. The pleura was irregularly and diffusely thickened by a blastomatous layer, firm, white-pinkish with yellow spots, that covered the entire surface of the lung. The tumor-like layer, had various degrees of thickness, more evident on the

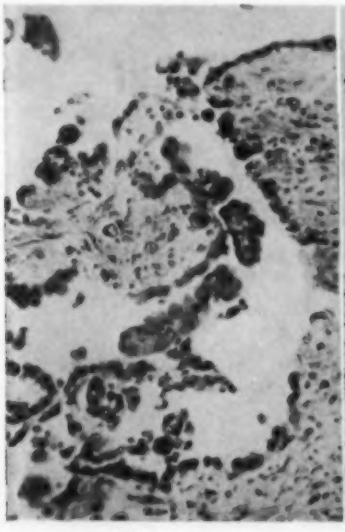


FIGURE 3

FIGURE 4

diaphragmatic and inferior mediastinal aspects. The cut surface showed the pleura, one to five centimeters thick, over the whole surface of the lung, including the interlobar aspect. The blastomatous tissue contained small cystic cavities filled with sticky, mucoid-like fluid. The subjacent lung was collapsed but not invaded. A careful examination of the bronchi failed to show localized tumor (Fig. 2).

Microscopical specimens taken from various areas of the neoplastic mass, showed different histological pictures: papillary and glandular arrangement, or irregular solid nests of atypical cells, or isolated malignant cells between the described pictures. Sometimes the glandular-like structures were cystically dilated; in other areas the cells were oval and circularly arranged, with a general lymphoangiomatous shape. The cells that formed these structures were mostly cubical, with a small amount of cytoplasm. The nuclei were oval, uniform in size, shape, and were vesicular with one or two nucleoli.

Cylindrical, polygonal, round cells, with or without mycotic figures, were seen in all specimens. In the solid nests the cells were pleomorphic. The Schiff staining of some specimens showed no evidence of mucine. The trostroma in some areas was oedematous and cellular in other places. The lung, adjacent to the involved pleura, was atelectatic but not invaded (Figures 3 and 4). Diagnosis:—Diffuse malignant mesothelioma of the pleura.

He did well until April, 1954, when an abdomino-thoracic tumor was discovered which caused pain and ascitis. This situation became progressively worse, until he died in June, 1954. Autopsy was not performed.

REFERENCES

1 Adorni, O., Goyeches, J., Negrete, D. H. and Eguia, O.: "Consideraciones clinico patologicas sobre un caso de tumor primitivo de la pleura," *Semana Medica*, 99:659, 1951.
2 Biggs, H. M.: "Endothelioma of the Pleura," *Proc. New York Path. Soc.*, 119, 1890.
3 Benoit, H. W., Jr. and Ackermann, L. V.: "Solitary Pleural Mesotheliomas," *J. Thoracic Surg.*, 25:346, 1953.
4 Bogardus, G. M., Kundtsun, K. P. and Mills, W. H.: "Pleural Mesothelioma," *Am. Rev. Tuberc. and Pulm. Dis.*, 71:280, 1955.
5 Dell'Acqua, G.: "Mesoteliomi della pleura; polimeioteliomi," *Acad. Med.*, 66:133, 1951.
6 Friedmann, L. L.: "Tumors of the Pleura," *Dis. Chest*, 17:756, 1950.
7 Gunn, F. D. and Anderson, W. A.: *Pathology*, C. V. Mosby Co., 1948.
8 Hertzog, A. J.: "Mesothelioma of the Pleura," *Minnesota Med.*, 28:209, 1945.
9 Hochberg, L. A.: "Endothelioma (Mesothelioma) of the Pleura: A Review with a Report of Seven Cases, Four of Which Were Extirpated Surgically," *Am. Rev. Tuberc.*, 63:150, 1951.
10 Jenny, E. R. and Ulsperger, O.: "Die intrathorakalen sog. Endotheliome," *Langenbecks Arch. u. Deut. Zschr. Chir.*, 278:376, 1954.
11 Lindskog, G. and Liebow, A.: *Thoracic Surgery and Related Pathology*, New York. 1953, page 75.
12 Piatt, A. D.: "Primary Mesothelioma (Endothelioma) of the Pleura," *Am. J. Roent.*, 55:173, 1946.
13 Stout, A. P. and Murray, M. R.: "Localized Pleural Mesothelioma," *Arch. Path.*, 34:951, 1942.
14 Stout, A. P.: "Solitary Fibrous Mesothelioma of the Peritoneum," *Cancer*, 3:280, 1950.
15 Tavares de Lima, M. L., San Juan, E. and Zerbini, E. J.: "Mesothelioma da pleura," *Rev. Med. Cir. São Paulo*, 14:31, 1954.
16 Wagner, E.: "Das Tuberkulahnliche Lymphadenoma," *Arch. d. Heilk.*, 11:495, 1870.
17 Weissmann, H.: "Primary Endothelioma of the Pleura," *Dis. Chest*, 12:562, 1946.
18 Whitehead, R. E.: "Mesothelioma of the Pleura," *Dis. Chest*, 17:569, 1950.
19 Willis, R. A.: *Pathology of Tumors*, C. V. Mosby Co., 1948.
20 Yesner, R. and Hurwitz, A.: "Localized Pleural Mesothelioma," *J. Thoracic Surg.*, 26:325, 1953.

Chylothorax as Complication in Pulmonary Resection*

EUDARDO SAENZA JIMENEZ, M.D.
Cartago, Costa Rica

and VICENTE LOPEZ MAJANO, M.D.
Mount Wilson, Maryland

Traumatic chylothorax, described by Quincke in 1875 is an unmistakable and infrequent condition (hardly more than 100 cases have been reported). Some of them are caused by contusions of the chest or back, fractures of the left clavicle or ribs, hyperextension of the vertebral column, thoracoplasty with apicolysis, operations to correct congenital heart defects, operations on the esophagus, etc. But in the great series of pulmonary interventions we did not find reference to chylothorax as a complication of pulmonary resection. Our experience includes two cases of chylothorax: one that subsided spontaneously in a few hours and one that is the object of this report. The first one occurred in a patient with a destroyed lung that was subject to left pleuropneumonectomy; some chyle was collected after the operation. It is to be noted that after awaking this patient had ingested great quantities of milk and cream.

There is no agreement on therapeutic conduct in cases of traumatic chylothorax, some authors advising periodical punctures, with or without intravenous infusion of the recovered chyle. Phrenicopraxis and pneumoperitoneum were considered when Florer and Ochsner reported, in 1945, an operative mortality of 100 per cent when trying to repair the conduct. Recently some authors favor tying, others repairing or anastomising the conduct to a vein, the main difficulty consisting in recognizing the thoracic conduct. Administration of food rich in fat or lypophilic dyes can help identify the thoracic conduct and determine the exact point of rupture. The decrease in mortality among patients operated for chylothorax is due to such factors as the general practice of intervening seven to 14 days after the trauma (before inanition or collapse may develop), improved anesthetic and surgical technics, antibiotics and careful postoperative attention.

Case Report

C. L. P., a white man 22 years old entered the Sanatorio Duran (Costa Rica) for the first time in April 1942. The diagnosis was: bilateral, moderately advanced pulmonary tuberculosis, with Pinner II excavation in the right upper lobe and acino-nodulous lesions disseminated in both upper lobes, active, slowly progressive. He was discharged, apparently cured, in May 1943. He reentered the hospital in March 1946 with bilateral reactivations of the initial lesions, excavations Pinner II in both upper lobes, with multiple calcifications in the left upper lobe.

Treatment: He had bilateral intrapleural pneumothorax; adhesions were severed twice. After reexpansion there remained residual necrotic foci and moderate paquipleuritis. Right extrapleural pneumothorax was maintained for one year; the sputum remained positive and the excavation persisted. Reexpansion was accompanied by intense paquipleuritis, exudate and upper mediastinal retraction. Pneumoperitoneum

*From the Sanatorio Duran.

was administered for 13 months. Antituberculous drugs had been administered since 1949. Failure of various procedures left no alternative to resection of the right upper lobe, decortication and thoracoplasty.

On August 11, 1954 liberation of the right upper lobe was extremely laborious on account of paquipleuritis of 3 to 6 millimeters, with adhesions to the costal surface and mediastinum. The cavity in the anterior segment was accidentally opened while removing the right upper lobe; decortication of the remaining lobes was done resulting in ruptures in the lower lobe which were not sutured. The intended thoracoplasty was not performed in view of the bad condition of the patient. Some 30 hours after the operation a milky liquid mixed with blood exuded through the drainage tubes. Forty-six hours after the operation, after the suction has been interrupted for 30 minutes, 1500 cc. of this liquid collected. The laboratory findings were: color milky white; specific gravity 1021; does not coagulate; total proteins 4.5 per cent; soluble in ether; can be dyed with Sudan III; 97 per cent of lymphocites without centrifugalization; sterile to Gram and Ziehl; cultures negative.

Temporary interruption of thoracic aspiration was accompanied by intense subcutaneous emphysema in the face, neck and thorax. Forty-seven hours after the operation, thoracoscopy was performed through the second anterior interspace, in a semi-seated position. The lung was partially atelectatic, covered with hemo-fibrinous material. On the mediastinum and the lung there was chylous liquid descending from the hilum by force of gravity; its exact point of origin could not be found; vascular ligatures and bronchial sutures were intact. During the next 48 hours the chyle continued to flow at the rate of about 1000 cc. in 24 hours. Seventy-two hours after the discovery of the chylothorax thoracotomy was performed; the remaining lobes were found half expanded, covered with fibrinous material, with two filtrating ruptures of 5 centimeters in the posterior basal and the diaphragmatic surface of the basal group. There was 400 cc. of chyle. The ruptures were approximated with continuous suture with atraumatic silk 4-0. Reexpansion was satisfactory.

Careful examination of the mediastinum did not reveal the origin of the chyle that ceased to flow after the thorax has been opened. A blind stitch, however, was made between the aorta, azygos and esophagus, close to the body of the eighth dorsal vertebra, in an attempt to include the thoracic conduct near its entrance to the thorax. Subperiostic resection from the sixth to the second rib was performed. The recovery of the patient was satisfactory and no more drainage of chyle was observed.

The traumatic chylothorax, in the related case, might have been due to a rupture of the thoracic conduct during the efforts to free the lung from the pleura. Assuming that this was a possible mechanism of the accident, we have tried to tie the thoracic conduct with a blind stitch. Since, however, anatomic anomalies of the thoracic conduct are highly frequent, and, above all, in view of the existence of tearings in the remaining lobes, a continuous suture of the lacterated parenchyma and thoracoplasty were performed to produce a compression and later, the adhesion of the sutures.

Present Status of Chemotherapy in Tuberculosis

Report of Committee on Chemotherapy and Antibiotics

American College of Chest Physicians

As in previous years this report is not intended as a detailed treatise for chemotherapy of tuberculosis, but rather as a progress report or statement on currently accepted principles and practice to serve as a guide to the physician treating tuberculosis.

General Considerations

At this writing there is no generally accepted optimum regimen in the chemotherapy of pulmonary tuberculosis. Streptomycin (SM), aminosalicylic (PAS) formerly para-aminosalicylic acid, USP XIV, and isoniazid (INH) are the three most commonly used drugs, but there is no unanimity of opinion as to which combination of these is most effective. However, it is emphasized that the best results are obtained when two or more drugs are combined and given continuously for a prolonged period of time. In general, it is probably unwise ever to treat a case of clinically active tuberculosis with one drug alone unless other drugs are contraindicated. Chemotherapy should be given for at least a year even in minimal cases and in advanced cases for a total of 18 to 24 months or at least until the stage of inactive disease is reached.

In all cases of tuberculosis, efforts should be made to culture the tubercle bacilli initially and to determine drug susceptibilities. This is essential in re-treatment cases. Susceptibility studies are especially important if cultures remain positive for changes in drug therapy may be based on changes in susceptibility.

Specific Drugs

The following drugs are useful in treating tuberculosis:

Isoniazid is a potent drug. It is effective at low concentrations, is readily absorbed, and penetrates all tissues of the body. It is easily administered and is relatively nontoxic with good patient acceptance. The most commonly accepted dosage of INH at the present time is 4 to 5 mg. per kg. of body weight daily, in two or three divided doses. It is estimated that some individuals will have inadequate serum levels of INH as measured by bio-assay on this dosage level. Evidence is at hand that about 85 per cent of patients with new tuberculosis will do well on standard doses of INH (300 mg. per day) in combination with other effective drugs. In the other 15 per cent, particularly in patients with more advanced disease with large or multiple cavities, it is probably advisable to individualize the dosage of the drug with consideration given to higher dosage. Toxic effects of this drug, particularly peripheral neuritis, are commoner at the higher levels and pyridoxine (100 mg. per day) must be administered con-

currently whenever the higher dosages are to be used. Hypersensitivity reactions may occur in the use of this drug as with streptomycin or PAS.

There are two major facts to be kept in mind in the use of INH: (1) As with most of the other effective drugs the tubercle bacilli readily becomes resistant to this drug when it is administered alone; (2) Isoniazid is degraded in human subjects into several derivatives such as acetylisoniazid which are biologically inactive; such inactivation varies significantly from individual to individual. Serum levels of this drug determined by the standard chemical methods will not reveal the inactivation, but it will be evident if bio-assay methods are used.

Streptomycin and Dihydrostreptomycin continue to be among the most effective antituberculosis agents at our disposal. Each has the same therapeutic value and the dosage is the same for both. They are generally administered in a dosage of at least 1 gm. twice weekly by intramuscular injection. In this dosage streptomycin rarely causes vestibular damage and dihydrostreptomycin rarely results in deafness. In an effort to avoid these rather remote possibilities some physicians prefer a combination of streptomycin 0.5 gm. and dihydrostreptomycin 0.5 gm. In studies reported by the British Medical Research Council it was evident that, when administered in combination with daily INH, streptomycin was more effective in preventing the emergence of INH resistant organisms when given in daily dose of 1 gm. as compared with dose of 1 gm. twice weekly. Preliminary reports are appearing indicating that in some patients, particularly those with advanced disease, intermittent streptomycin may be less effective than daily administration of 1 gm. of this drug. It may be advisable to give streptomycin in doses of 1 gm. daily for at least 30 days to a patient severely ill on admission before reverting to intermittent therapy. Hypersensitivity to streptomycin occurs occasionally and is manifested by fever, rash and sometimes exfoliative dermatitis. In patients with less severe reactions desensitization may be accomplished by starting with a very small dose and gradually increasing; with more severe reactions desensitization may be hazardous and probably should not be attempted. Occasionally, a patient hypersensitive to streptomycin may be able to tolerate dihydrostreptomycin and vice versa.

Aminosalicylic Acid remains an important agent in the antimicrobial therapy of tuberculosis due to its ability to prevent or postpone resistance to streptomycin and INH; and to its ability to enhance the serum levels of active INH. Many forms of this drug are on the market from the acid product to sodium, potassium and calcium salts of the acid, a buffered product, and other forms. The dosage for all of these must be adjusted to the dose of the acid. In other words, 15 gm. of sodium PAS is the equivalent to 12 gm. of acid PAS. Many patients will have less gastrointestinal intolerance on some one of these products than on others. There is some difference in blood levels produced with these drugs. Sodium and potassium PAS being rapidly absorbed have rapid peaking and falling off of blood levels, while with other forms a more prolonged peak may be attained. The clinical significance of this is undetermined at the present time.

PAS preparations of all types if stored too long or exposed to undue heat, light or moisture, deteriorate and discolor, resulting in increased intolerance or actual toxicity. PAS should be prepared fresh if given in solution. Under best conditions, side reactions of anorexia, nausea and diarrhea are not uncommon with all forms of PAS, but are not necessarily indications for discontinuing the drug. Occasional patients develop more severe reactions with fever, rash and rarely with severe systemic reactions simulating infectious mononucleosis.

PAS alone is relatively not very effective as a treatment for tuberculosis and should always be used in combined therapy. It has been shown recently that PAS, when administered concurrently with INH, will enhance the level of free INH in the serum of patients who rapidly inactivate INH. In Europe intravenous PAS is being used extensively and claims have been made for its value by this route.

The standard dose of PAS in this country is 12 gm. daily in three divided doses, although some studies have indicated that smaller doses of the active substance may well be useful, particularly if full dosage is not tolerated.

Viomycin has a useful though rather limited place in the treatment of the patient whose organisms are resistant to isoniazid and streptomycin and for whom an umbrella is desirable for resectional surgery. The usual dosage is 2 gm. (IM) twice weekly for two or three weeks before surgery and eight to ten weeks or more postoperatively. When feasible it should be combined with another drug to which the organisms are sensitive. Renal toxicity precludes the daily use of this drug, but is less evident when used twice weekly.

Pyrazinamide (PZA) is now undergoing clinical investigation by the Veterans Administration—Armed Forces group, the USPHS group, and others, particularly in combinations with isoniazid. It has been found to be effective in combination with INH when administered to patients who have never received either drug before. There is some evidence that this drug may be effective for short periods of 30 to 60 days when used alone, particularly to cover resectional surgery in patients resistant to the other major drugs. In most studies reported, there has been a significant factor of toxic effect on the liver; approximately 10 per cent of the patients receiving pyrazinamide have shown abnormal results in liver function studies and about 3 per cent have shown frank jaundice. When this drug is administered liver function studies should be done periodically to estimate any liver toxicity. Most of the toxic conditions resulting from the use of this drug, however, revert to normal when the drug is withdrawn. PZA should be discontinued promptly if significant disturbance in liver function is noted and invariably if jaundice appears. At the present time, due to severe toxicity of the drug, it should be administered only to patients in the hospital. This drug is ordinarily administered in dosage of from 30 to 40 mg. per kg., orally administering no more than 3 gm. daily. Hyperuricemia has been reported in conjunction with the use of PZA.

Cycloserine is a relatively new antibiotic under investigation for use in the treatment of tuberculosis. Preliminary studies have shown that this

drug used alone is not as effective in the treatment of tuberculosis as are the various combined drug regimens now in use. At present, studies are in progress to determine the effectiveness of this drug when used in combinations with INH. Reports of toxicity, particularly to the nervous system, have continued such as tremors, drowsiness, convulsions and psychoses. Most investigators originally used this drug in dosage of 1 gm. daily, orally, in divided doses. Newer studies indicate a maintenance of therapeutic effectiveness and nearly complete absence of toxicity when administered in doses of 0.25 gm. twice daily in combination with isoniazid.

Recommended Regimens: Though there is no generally accepted optimum chemotherapy regimen for pulmonary tuberculosis at the present time recent reports of the Veterans Administration—Armed Forces Group and of U. S. Public Health Service sponsored studies indicate that the following regimens give approximately the same clinical results in most cases of tuberculosis: (1) Isoniazid, 300 mg. daily plus PAS 12 gm. daily; (2) Isoniazid 300 mg. daily plus SM 1 gm. twice weekly, and (3) Isoniazid 300 mg. daily plus SM 1 gm. twice weekly plus PAS 12 gm. daily. The Veterans Administration and U. S. Public Health Service studies indicate that the regimen of streptomycin 1 gm. twice weekly and PAS 12 gm. daily is not quite the equal of the other three regimens, and that in far advanced disease with large cavities INH-PAS is superior to intermittent SM-INH.

As has been pointed out above, there is increasing evidence that the drug regimens must be individualized in certain patients, particularly in those with more advanced disease, with larger doses of INH and daily SM being administered as indicated.

Acute Miliary Tuberculosis

Isoniazid has proved to be very effective in the treatment of miliary tuberculosis with survival rates of 90 per cent and higher being reported. Any standard INH containing combined regimen should be adequate in treating this condition, but due to the serious nature of miliary tuberculosis many still advocate the use of triple drug therapy with higher dosages of isoniazid such as 10 mg. per kg. per day being used. The drug therapy should be continued for at least 18 months.

Tuberculous Meningitis

Reports during the past several years indicate that survival rates of 80 per cent to 90 per cent or higher are possible in tuberculous meningitis when INH, SM and PAS are administered for a minimum of 24 months. The Committee suggests a dosage schedule similar to that for miliary tuberculosis. Intrathecal medication is not recommended. It is of the utmost importance to start the treatment immediately if the history, physical examination or spinal fluid findings strongly suggest a diagnosis of tuberculous meningitis. If the patient's condition does not permit oral medication, the INH and PAS may be given parenterally, initially.

Genitourinary Tuberculosis

Genitourinary tuberculosis responds very well to combined drug therapy including INH, SM and PAS in dosage as recommended for pulmonary tuberculosis. The drug should be administered for 18 to 24 months. Recent reports from the Veterans Administration—Armed Forces study indicate that long-term therapy with INH, SM and PAS is very often definitive in such cases and the need for surgical intervention is becoming surprisingly less frequent.

Tuberculosis in Childhood

The Committee recommends that all children with active primary tuberculosis should receive antimicrobial therapy. The complications such as miliary and meningeal tuberculosis which sometimes occur in primary disease have sharply declined since the advent and use of INH. Consideration should be given to the treatment of recent tuberculous converters, particularly in children under four years of age. In children with active tuberculosis, the physician should always be on the alert for the development of miliary or meningeal tuberculosis. The approximate dosages of the antituberculosis drugs for children are as follows: SM 30 to 40 mg./kg. twice weekly, INH 10 to 16 mg./kg./day and PAS 200 mg./kg./day. Children tolerate higher dosages of INH well and administration of pyridoxin is usually not needed to prevent toxicity.

Other Forms of Tuberculosis

When the disease involves such organs and tissues as the larynx, mouth, lymph nodes, trachea, bronchi, GI tract and bone it is best treated by long term combined chemotherapy using one of the regimens recommended for pulmonary tuberculosis.

Tuberculous Pleurisy with Effusion

This condition should be treated as a case of active pulmonary tuberculosis with long term continuous combined chemotherapy for a year or more. This recommendation also applies to the so-called idiopathic pleurisy with effusion patients with a positive Mantoux even though careful studies fail to reveal presence of tubercle bacilli in the pleural fluid. Experience has shown that in such cases the etiology is usually tuberculous and should be treated as such in order to avoid reactivation later.

Steroid Therapy in Tuberculosis

The exact role of cortisone and related compounds in the management of infectious diseases is undefined. However, the greatest difference of opinion regarding the place of steroids exists in the field of tuberculosis. Some have felt that this form of therapy is always contraindicated while others have recommended its use under certain specific circumstances. Some of the tissue damage and clinical manifestations in tuberculosis are due to an exaggerated interaction between sensitized tissue and tuberculoprotein.

Corticosteroids may suppress this overactive defense mechanism with a resulting decrease in the manifestations of illness. In patients seriously ill with tuberculosis of long duration there is evidence of adrenocortical hypofunction. Steroid therapy used with concomitant antituberculosis chemotherapy often effects striking symptomatic improvement. Thus, without anticipating any change in the ultimate outcome, the use of steroids would appear to be justified, if only for its symptomatic effect, in patients hopelessly ill with advanced tuberculosis. In acute forms of tuberculosis associated with severe clinical illness, steroids may be helpful. This is especially true of miliary and meningeal tuberculosis. In the latter condition, prevention and relief of cerebrospinal fluid block has been attributed to steroids.

Committee on Chemotherapy and Antibiotics
American College of Chest Physicians

James A. Wier, Denver, Colorado.....Chairman
H. Corwin Hinshaw, San Francisco, California.....Vice-Chairman
Sumner S. Cohen, Oak Terrace, Minnesota.....Secretary

James O. Armstrong, Dallas, Texas
Benson Bloom, Tucson, Arizona
Philip A. Boyer, Jr., Indianapolis, Indiana
James Cullen, Albany, New York
Edward Dunner, Washington, D. C.
Israel G. Epstein, Brooklyn, New York
George F. Evans, Clarksburg, West Virginia
Michael L. Furcolow, Kansas City, Kansas
Joseph L. Geraci, Rochester, Minnesota
Alfred Goldman, St. Louis, Missouri
Nathan Goldstein, New Orleans, Louisiana
W. Leonard Howard, Northville, Michigan
Sol Katz, Washington, D. C.
Maurice D. Kenler, New Bedford, Massachusetts
George O. Kress, Columbus, Ohio
Ruben Laurier, Montreal, Quebec
Joseph H. Lee, Hamilton, Ontario
Meyer R. Lichtenstein, Chicago, Illinois
Charles E. Lyght, Rahway, New Jersey
George E. Martin, Pittsburgh, Pennsylvania
Robert L. Mayock, Philadelphia, Pennsylvania
Ralph E. Moyer, Oteen, North Carolina
John B. Plum, Fort Sam Houston, Texas
Edward S. Ray, Richmond, Virginia
Edward H. Robitzek, Staten Island, New York
Louis I. Sokol, Los Angeles, California
Kent H. Thayer, Phoenix, Arizona

World Peace Promoted by Physicians

Although it is probable that much of the content of the Hippocratic oath had long been in use and that Hippocrates added his own concepts and practices, "it is the method of Hippocrates, the use of the mind and senses as diagnostic instruments, together with his transparent honesty and his elevated perception of the dignity of the physician's calling, his high seriousness and deep respect for his patients, that make him, by common consent, the 'Father of Medicine,' and the greatest of all physicians."

Throughout the centuries, the Hippocratic oath has been read by students and graduates in medicine, and its high ethical code has had a strong influence in the promotion of mutual understanding and practices of physicians throughout the world. Major says ". . . its lofty tone and ethical precepts represent a spirit that lifted medicine to the status of a learned and noble profession and also one conscious of its own limitations."

Hippocrates said, "Where there is love for mankind, there is love for the art of healing. The prime object of the physician in the whole art of medicine should be to make the sick well, and, while it is possible to make the sick well by various means, one should choose the method producing the least spectacular, since this is a rule both of honor and of our art, for one does not seek unsavory public acclaim."

The 1,500,000 physicians serving the 2,700,000,000 citizens of the world today have, for the most part, come under the influence of the Hippocratic oath. Their common purpose is to help people everywhere experience the great desires of all, namely, to enjoy good health, to live happily, to live long, and to contribute to the good of humanity.

Thus, the goal of physicians is to promptly come to the aid of those suffering from disease, congenital abnormality, inherited conditions, etc., and to repair bodies damaged by violence both in peace and war so such conditions, in as far as possible, may be driven from the earth.

Regardless of race, nationality, color, religion, or politics, human bodies, except for differences in stature, are the same the world over. Diseases that attack them, as well as their treatment and control, are essentially the same.

Through the centuries many physicians have worked feverishly to find new and better methods of diagnosing, treating, and controlling diseases, repairing wounds, etc. Much of the diagnostic and some of the therapeutic armamentarium of today were discovered or produced by pure scientists, such as the microscope by the Jansen's, Holland, the x-ray by Roentgen, Germany, para-aminosalicylic acid by Lehmann, Sweden, and streptomycin by Waksman, United States.

Ethical physicians and scientists have no secrets. Anything found to be beneficial in treatment, control and prevention of disease is flashed to the medical profession of the world. When Robert Koch discovered the tubercle bacillus and produced tuberculin, his methods were published and the

journals containing them were dispatched to the various nations. Transportation was slow, and in some instances months were required before the journals arrived in other lands. An important new discovery announced today may be described by radio in all nations within hours.

Assembling of two or more physicians to discuss medical problems, exchange viewpoints, present new materials, etc., has long been recognized as an exceedingly satisfactory means of transmitting and receiving new information. Hence the regular meetings of county, state, national and international medical organizations.

Physicians of the last century recognized tuberculosis as a worldwide problem and saw the value of international meetings. The first international congresses on tuberculosis were held in Paris in 1867 and 1888. Four more occurred in European cities during the 1890's. As the 20th century opened, one was held in London, another in Paris, and one in Washington D. C. (1908). These international meetings were suspended during World War I, but they were resumed biannually, mostly in Europe, after the war under the name International Union Against Tuberculosis. They were also suspended during World War II and resumed in 1946. As the name indicates, the International Union Against Tuberculosis has dealt with that disease. This has been a most laudible activity and should remain so for any decades because tuberculosis is still number one among the communicable diseases causing incapacity and death in the world as a whole.

More recently, it became obvious that other chest diseases needed consideration on a worldwide basis. Therefore, the American College of Chest Physicians, which was founded in 1935 and had worked with medical groups in other nations, organized the first International Congress on Diseases of the Chest which was held in Rome, September 17 to 22, 1950. Approximately 1,000 persons registered and physicians from 43 nations assembled for sessions at the Carlo Forlanini Institute. Dr. Eugenio Morelli, Founder, and Dr. A. Omodei Zorini, Medical director, Carlo Forlanini Institute, served as co-chairmen for this first congress.

The second International Congress on Diseases of the Chest in Rio de Janeiro, Brazil, was presented the same week as the meeting of the International Union Against Tuberculosis whose sessions were August 25, 26, and 27 and those of the International Congress on August 28, 29, and 30, 1952. The meetings were presided over by Dr. Manoel de Abreu, whose name was already household among chest disease workers around the world because of his work in photofluorography.

The third International Congress was held in Barcelona, Spain, October 4 to 8, 1954, where the registration exceeded 2,000, representing 59 countries and territories. Dr. Luis Rosal and Dr. Antonio Caralps presided over this important congress.

The fourth Congress was held in Cologne, Germany, August 19 to 23, 1956. Dr. Gerhard Domagk of worldwide renown for contributions to knowledge of anti-microbial drugs was president of this congress. More than 2,100 persons registered from 58 countries and territories.

During these congresses, many physicians met one another whom they had previously known only through medical literature or not at all. Personal friendships were established with much deeper subsequent interest in one another's work and writing. They heard manuscripts read before publication, participated in asking authors questions and discussing their papers. They met some of the world's most famous physicians engaged in chest disease work. For example, in Rome Dr. A. Omodei Zorini, Medical Director, conducted personal tours through the Forlanini Institute and presented clinics.

To see and hear a man whose name was most frequently mentioned at that time around the world, Sir Alexander Fleming, was a unique experience. At that Congress it was stated that his work and his methods followed by others had resulted in an increase in the span of human life of approximately 10 years.

During the interim session of the American College of Chest Physicians held in Miami Beach, November, 1954, Dr. Arnold S. Anderson, St. Petersburg, Florida informally expressed his evaluation of all such meetings with reference to world peace. His editorial, "Doctors and Peace" in the June, 1955 issue of *Diseases of the Chest* was immediately popular and has resulted in such wide approbation as to suggest a series of editorials on the general theme of the influence International Congresses may have on the peace of the world.

Dr. Paul D. White, Boston, recently said, "Cooperative international cardio-vascular or other medical research should ultimately result not only in greater knowledge which will help all of us all over the globe, but should also establish international friendships and foster eventually international peace. We doctors have perhaps only a small role to play in such an opportunity, but small as it is let us play it. I often feel that if we physicians could take over international relationships, peace could descend upon the world. This may be a far cry from reality, but nevertheless, physicians do take care of leaders in business, in the professions, and in government throughout the world. Thus, they do have, willy-nilly, an important responsibility which is not that of playing politics, but that of helping to establish friendly relations in a completely impartial way."

This is the first of a series of editorials prepared by physicians stationed in various parts of the world. Physicians from all nations are invited to prepare and submit material for this series and as many will be published as time and space permit.

J. Arthur Myers
Editor

College News

INTERIM SESSION

The Interim Session of the College will be held at the Warwick Hotel, Philadelphia, on Monday, December 2. A scientific session, sponsored by the Pennsylvania Chapter, is being organized under the chairmanship of Dr. Robert V. Cohen, in which a splendid group of eminent speakers will participate.

A number of formal papers will be presented in the morning session, to be followed by a panel discussion on a timely subject. At noon several interesting round table luncheon discussions are being planned. The afternoon session will consist of several formal presentations and another panel discussion. The Pennsylvania Chapter will be host at a cocktail party preceding a dinner on Monday evening. The meeting will close with a session of Fireside Conferences that evening. The complete program will be published in an early issue of the journal and it is hoped that all members of the College will plan to attend this excellent meeting.

The Board of Regents and the Board of Governors will hold their semi-annual meetings at the Warwick Hotel on Tuesday, December 3, and a number of councils and committees of the College will also meet on that day. Examinations for Fellowship in the College will be given on December 3 under the direction of the Board of Examiners.

The Clinical Meeting of the American Medical Association will take place in Philadelphia, December 3 through 6. Reservations may be obtained by writing directly to the Warwick Hotel, Philadelphia. Please be sure to give arrival and departure dates, and mention that you will attend the meeting of the American College of Chest Physicians.

1958 ANNUAL MEETING

The 24th Annual Meeting of the College will be held at the Fairmont Hotel, San Francisco, June 18-22, 1958. The Committee on Scientific Program, under the direction of Drs. Samuel Bellet and Peter A. Theodos, is now in preparation. Physicians desiring to present their work are urged to submit a 200-word abstract at the earliest possible date. October 15 is the deadline date for receipt of abstracts to be considered by the committee. Please forward abstracts to the appropriate co-chairman:

Dr. Samuel Bellet, 2021 Spruce Street, Philadelphia, Pennsylvania
Chairman, Section on Cardiovascular Diseases

Dr. Peter A. Theodos, 1930 Chestnut Street, Philadelphia, Pennsylvania
Chairman, Section on Pulmonary Diseases

Other members of the Committee on Scientific Program are:

Pulmonary Section: Seymour M. Farber, San Francisco; R. Drew Miller, Rochester, Minnesota; Emil A. Naclerio, New York City; Coleman B. Rabin, New York City; Elmer C. Rigby, Los Angeles; James A. Wier, Denver; Karl H. Pfuetze, Chicago, (ex-officio).

Cardiovascular Section: Milton W. Anderson, Rochester, Minnesota; Benjamin M. Gasul, Chicago; Charles A. Hufnagel, Washington, D. C., Fay A. LeFevre, Cleveland; Arthur M. Master, New York City; John J. Sampson, San Francisco.

Chapter News

INDIANA CHAPTER

The Indiana Chapter will hold its annual meeting on October 8 at the French Lick Sheraton Hotel, French Lick Springs, in conjunction with the Tuberculosis Committee of the Indiana State Medical Association. After luncheon, the following program will be presented:

Business meeting and election of officers

"Non-tuberculous Suppurative Diseases of the Lungs"
Stuart R. Combs, Terre Haute

X-ray symposium

NEW JERSEY CHAPTER

The annual fall meeting of the New Jersey Chapter will take place on October 15 at the State Medical Society building in Trenton at 8:30 p.m. The program will be devoted to papers dealing with the diagnosis and therapy of cardiovascular diseases amenable to surgery.

POTOMAC CHAPTER

The annual meeting of the Potomac Chapter will be held at the Hotel Emerson, Baltimore, Maryland, Sunday, October 20. The following program will be presented:

9:00 a.m. Registration

10:00 a.m. "Pathological Aspects of Coronary Disease"
George W. Vandegrift, Baltimore

"Medical Management of Coronary Artery Disease"
William S. Love, Baltimore

"Surgical Aspects of Coronary Artery Disease"
James H. Walker, Charleston, West Virginia

Panel discussion—"The Advantages and Disadvantages of General vs. Local Anesthesia in Peroral Endoscopy"

Moderator: John H. Hirschfeld, Baltimore

Panel: Donald F. Procter, Elliott Michelson, and Peter Safar, Baltimore

12:00 noon noon Luncheon. Guest speaker—Donald R. McKay, Buffalo, New York, President-Elect, American College of Chest Physicians

2:00 p.m. Panel discussion—"Surgical Management of Chest Trauma"

Moderator: Emil A. Naclerio, New York City

Panel: James G. Arnold, Charles N. Davidson, and Donald B. Hebb, Baltimore

"Medical Management of Pulmonary Emphysema"
Warde B. Allen, Baltimore

"Surgical Treatment of Pulmonary Emphysema"
Otto C. Brantigan, Baltimore

X-ray Conference

VIRGINIA CHAPTER

The Virginia Chapter will hold its annual meeting at the Shoreham Hotel, Washington, D. C., on October 27. The following program will be presented:

2:00 p.m. "Case-finding of Pulmonary Disease"
Katharine R. Boucot, Philadelphia, Pennsylvania

"Cardiac Emergencies, The Diagnosis and Treatment"
Julian Beckwith, Charlottesville, Virginia

"Treatment of Emphysema"
George E. Ewart and C. F. Wingo, Richmond, Virginia

4:00 p.m. Business meeting

ARGENTINE CHAPTER

At the annual meeting of the Argentine Chapter, held in Parana recently, the following officers were elected:

President:	Jose Peroncini, Buenos Aires
Vice-President:	Oscar Izaquirre, Parana
Secretary-Treasurer:	Bruno A. Biondini, Buenos Aires

ISRAEL CHAPTER

The annual meeting of the Israel Chapter was held in Tel-Aviv on July 11 and at the Meier Hospital, Kfar-Saba on July 12. The following program was presented:

"Epidemiology and Pathology of Sarcoidosis"
Joseph Rakower, Jerusalem
"Pathological Aspects of Sarcoidosis"
Erich Liban, Jerusalem
"Clinical Aspects of Pulmonary Sarcoidosis"
Chaim Einhorn, Tel-Aviv
"Cervical Biopsy in Sarcoidosis"
Kurt Friedmann, Tel-Aviv
"Esophagography in Thoracic Diseases"
Abraham Licht and Beinish Krzypow, Tel-Aviv
"Congenital Tuberculosis"
Pinchas Wayl, Jerusalem
"Tuberculosis in Old Age"
Wilhelm J. Hupert, Kfar-Saba
"Surgical Treatment of the Aged Patient"
Kurt Friedmann, Tel-Aviv
"Clinical Aspects in Tuberculosis Patients over 50"
Tuvia Levit, Beer-Yaacov
"The Aged Tuberculosis Patient in the Dispensary"
Rudolph Levi and Felix Krotowski, Tel-Aviv

The following officers were elected during the business meeting:

President:	Hermann Lichtenstein, Haifa
Vice-President:	Arthur Freund, Tivon
Secretary-Treasurer:	Wilhelm J. Hupert, Kfar-Saba

NEWS NOTES

Dr. Burgess L. Gordon, President of the American College of Chest Physicians, spoke on "The Evolution of Chronic Pulmonary Conditions in Older People" before the Bernalillo County Medical Society, Albuquerque, New Mexico, September 6.

Dr. Leo H. Rigler, formerly of Minneapolis, Minnesota, has been made consultant in radiology to Cedars of Lebanon Hospital, Los Angeles, California.

Dr. Alton Ochsner, New Orleans, Louisiana, spoke on "Bronchogenic Carcinoma" before a special meeting of the Hong Kong and China Chapter of the College, held on May 30 at the Hong Kong Sanatorium and Hospital. **Sister Mary Aquinas,** President of the Chapter, introduced **Dr. Li Shu-Fan,** Regent of the College for China, who presented Dr. Ochsner. Following the scientific program, Fellowship certificates were presented to **Dr. Phyllis Haddow** and **Dr. Ho Hung-Chiu.**

Dr. J. P. Medelman, St. Paul, Minnesota, is Councilor of the American College of Radiology for the Minnesota State Medical Society, representing the Fifth District.

Dr. Joseph K. Freilich, Chicago, Illinois, has been appointed Clinical Associate Professor of Medicine at the Chicago Medical School.

Dr. Philip Thorek, Chicago, Illinois, has received an award from the French medical publication, *La Presse Medicale,* for his educational film on infant surgery.

Dr. Otto L. Bettag, Chicago, Illinois, was elected President of the Medical Correction Association, the medical section of the American Prison Association.

Dr. Richard R. Trail, London, Regent of the College for England, has been appointed representative of the Ministries of Health and Labour of Great Britain at the World Veterans Federation Conference in Limoges and Paris, France, September 16-25.

Colonel Weldon J. Walker, formerly Chief of the Cardiovascular Service, Brooke Army Hospital, San Antonio, Texas, has been transferred to Europe where he will be Chief of the Department of Medicine at the 97th General Hospital and Consultant in Cardiovascular Diseases for the European Theatre of Operations.

ANNOUNCEMENTS

The IV Northern Brazilian Tuberculosis Congress will be held in Belem, November 15-19. Physicians from the South American countries, the United States, Portugal, and France will participate in the scientific program which will cover the following subjects:

Chest X-ray Surveys and Tuberculosis Morbidity
The Role of the Sanatorium in the Face of the Present Trends in the Anti-tuberculosis Fight
The Role of Surgery in the Therapy and Epidemiology of Tuberculosis

---

The next Laryngology and Bronchoesophagology course to be given by the University of Illinois College of Medicine is scheduled to be held November 4-16, 1957. The course is under the direction of Dr. Paul H. Holinger. Interested physicians should write to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

RESIDENT FELLOWS AVAILABLE

Applications for Resident Fellowships in Chest Diseases from qualified physicians in other countries have been received and approved by the Committee on Resident Fellowships. Following are brief resumes of the backgrounds of some of these applicants. The Executive Offices of the College in Chicago will be pleased to submit the original application forms and other pertinent information to interested physicians upon request.

YOA, Alexandria, Egypt, age 29, single (presently in this country). Premedical school: Faculty of Science, University of Alexandria '47; Medical school: University of Alexandria '53; Internship: University of Alexandria Hospital '54; Residencies: Tucson Medical Center, Arizona '54-'55; Sea View Hospital, New York '55-'56; Sunny Acres Hospital, Ohio '56 to present. Interested in medical aspects of chest diseases (heart and lungs).

SCB, Ranchi, India, age 50, single. Premedical school: Asutosh College '25; Medical school: Medical College of Calcutta '32; Internship: Medical College Hospital '32-'34; Residencies: Medical College Hospital '32-'34; Postgraduate: Vallabhai Patel Chest Institution '55-'56. Presently Senior medical officer, R. K. Mission Tuberculosis Sanatorium. Interested in all aspects of tuberculosis, including pathology.

TSF, Tainan, Free China, age 35, married. Premedical school: Yu Hsi High Middle School '38; Medical school: National Defense Medical Center '43; Internship: Army Medical College '43; Residency: Air Force Hospital '43-'48. Presently Chief Surgeon, Army Hospital. Interested in thoracic surgery.

GETR, Mexico City, Mexico, age 27, single (woman). Premedical school: Universidad Motolinia '47; Medical School: Facultad de Mexico; Internship: Hospital General de Mexico '52-'53; Postgraduate: Instituto Nacional de Cardiologia '54-'55, Sanatorio de Huipulco '53-'57. Presently electrocardiographer, Sanatorio de Huipulco and Hospital de la Cruz Roja. Interested in cardiopulmonary physiology.

OMS, Cairo, Egypt, age 33, single. Premedical School: Secondary School '42; Medical School: Kasr El Ainy Faculty of Medicine '49; Internship: University of Cairo Hospital '50; Residencies: Chest Section, University Hospital '50-52, Heliopolis Hospital '53; Postgraduate: University Hospital, Mobtdian Dispensary '52. Presently Clinical demonstrator, Chest Section, Faculty of Medicine. Interested in medical aspects of chest diseases.

Obituary

ROLLIN D. THOMPSON

1890-1956

Rollin Thompson was born at Black River Falls, Wisconsin in 1890—the same year as Koch announced tuberculin. He graduated from Black River Falls High School and at the age of 24 years, received the degree of Doctor of Medicine from the University of Illinois College of Medicine. During 1915, he interned at the Milwaukee County Hospital and the next year he was senior resident at Muirdale Sanatorium, Milwaukee, Wisconsin. He then engaged in private practice at Reedsburg, Wisconsin.

He was a lieutenant in the Medical Corps during World War I, with two years service overseas. Following the war he practiced general medicine at Baraboo, Wisconsin.

In 1925, he became Superintendent and Medical Director of the Kalamazoo County Sanatorium, Michigan but resigned in 1929 to accept a similar position with the Wisconsin State Sanatorium. In 1932, he was found to have pulmonary tuberculosis and was treated successfully at River Pine Sanatorium, Stevens Point, Wisconsin, and in due time returned to his position.

From 1937 to 1949, he was Superintendent and Medical Director of the Central Florida Tuberculosis Hospital at Orlando, and in 1946 he was named Superintendent and Medical Director of all Florida state tuberculosis hospitals. In 1949 and 1950 he held a similar position with La Vina Sanatorium, California. In 1950 and 1951, he was Superintendent and Medical Director of the Southeast Florida Tuberculosis Hospital at Lantana. Following 1951 he was Consultant in Tuberculosis to Veterans' Administration hospitals in Florida and to the United States Public Health Service.

While at the Central Florida Sanatorium, Dr. Thompson was elected to the presidency of the Southern Tuberculosis Conference, and in 1949 he became President of the National Tuberculosis Association.

Having taken a senior residency in a sanatorium and having suffered from tuberculosis requiring institutional treatment himself qualified Dr. Thompson admirably for a long life of service devoted largely to the diagnosis, treatment and prevention of tuberculosis. In addition to these fine qualifications, he was honest, sincere, and manifested great enthusiasm for his work.

During the early years of Dr. Thompson's career, much emphasis was placed on elicitation of rales in diagnosis. Post-tussic moderately coarse rales over the upper part of a lung were thought to be almost pathognomonic. A fair segment of the sanatorium physician's time was devoted to trying to control pulmonary hemorrhages and signing death certificates was a frequent duty. However, Dr. Thompson participated in advancing knowledge and lived to see and employ diagnostic, therapeutic, and preventive measures of today to his extreme satisfaction.

He was the first Superintendent and Medical Director of the newly-constructed Central Florida State Sanatorium. Having been invited by him to participate in the dedication ceremonies on January 3, 1938, I had the opportunity of seeing his sanatorium in complete operation and observing how perfectly he directed every detail of the institution. This occasion also provided an opportunity to meet with the Tuberculosis Committee of the State Medical Association and the State Sanatorium Board. Obviously, Dr. Thompson was influential with these groups in planning for more extensive work in tuberculosis throughout the state. He worked very closely with Dr. Arnold S. Anderson, St. Petersburg, who served for 16 years on the State Sanatorium Board. They and their colleagues inspired so much interest and activity as to result in Florida's present fine sanatorium system.

Dr. Thompson died at the Veterans' Administration Hospital, Coral Gables, Florida, on November 23, 1956. Dr. Anderson wrote, "We miss him very much. A part of the sanatorium system died with his passing." Dr. A. A. Pleyte, Milwaukee, so long and so closely associated with him in Wisconsin said, "Dr. Thompson's life was a full one. His contributions to medicine were many, his friends were numerous and his happy imprint on the lives of his family, his friends and his patients has endeared him to all who knew him."

J. Arthur Myers

Book Reviews

A PRACTICAL MANUAL OF DISEASES OF THE CHEST, by M. Davidson, M.D. Fourth edition, Oxford Medical Publications, 1954, 647 pages.

Following a chapter on the anatomy and physiology of the respiratory tract, diseases of the nasopharynx, larynx, bronchi, lung parenchyma, the pleura and mediastinum are presented. Tuberculosis is discussed in five chapters comprising 161 pages, about one-fourth of the text. The paper, printing and format are pleasing. Many of the illustrations have been selected with a critical eye and have been reproduced with commendable perfection. In matters pertaining to the management of lung diseases, the book carries a burdensome, antiquated mass of data which are confusing rather than helpful. This flaw detracts much of the practical value of this volume.

Andrew L. Banyai, M.D.

BRONCHOGRAPHY IN CHILDREN (LA BRONCOGRAFIA NEL BAMBINO), by Lucio Parenzan and Alfredo Vago. Supplement XXIII of the Archivio Italiano di Otologia, Rinologia e Laringologia, 1955 (In Italian; summaries in English, French, and German).

This is an authoritative contribution to the knowledge of lower respiratory pathology in children.

A new and safe technic of bronchography under general anesthesia is described with excellent results obtained in over 100 children. Several examples of normal anatomy and tracheo-bronchial topography are presented. The authors list the indications for bronchography in children as tracheo-bronchial pulmonary malformations, chronic broncho-pulmonary suppuration and primary tuberculosis.

Bronchography means team work between bronchoscopist, radiologist and anesthetist. It becomes the essential item of a triad of diagnostic procedures in lower respiratory pathology: laminography, bronchography and bronchoscopy. The authors suggest that even bronchoscopy should be "guided" by bronchography in children.

The exposition is clear and simple and many references are given. The monograph is amply documented by outstanding illustrations with explanatory diagrams making the reading extremely easy and enjoyable.

Elio J. Fornatto, M.D.

CRYPTOCOCCOSIS, by M. L. Littman, M.D. and Lorenz E. Zimmerman, M.D. Grune & Stratton, New York and London, 1956, $8.50.

Doctors Littman and Zimmerman are of the opinion that many cases of cryptococcosis are unrecognized, although only approximately 300 cases have been reported in the literature. This is borne out by the fact there is a wide discrepancy numerically in the published reports from various hospitals in the United States and in other countries. A short chapter on the source of infection and the portal of entry into the body suggests that the source of infection may be found in vegetable materials, foodstuffs and animals, and various portals of entry, although they believe the respiratory tract is the usual one. The human clinical aspects of cryptococcosis are well covered with illustrative case reports, photographs, autopsies, pathologic material and roentgenograms. Their discussion on the disease in animals tends to reveal important suggestions regarding the pathogenesis of cryptococcosis in man.

The most outstanding feature of the monograph deals with the pathology of cryptococcosis. Beautiful plates dealing with the microscopic and macroscopic appearance of the affected tissues have been painstakingly and carefully reproduced from a relatively large group of autopsied material. They stress that, although enlargement of the visceral organs to a degree that they are clinically evident is quite unusual, widespread microscopic lesions may be found. The section on laboratory studies includes the cytology of the fungus, direct examination of tissues and exudates, cultural studies, biochemical and physiologic reactions, botanical classification of C. neoformans and asporogenous yeasts, pathogenicity for animals, histopathologic diagnosis and criteria for identifiction of C. neoformans.

The final chapter on treatment and prognosis covers in detail our scant, definitive knowledge of the present day.

It is my opinion that the monograph on cryptococcosis by Drs. Littman and Zimmerman is the most complete survey of the subject published up to this time. I was impressed with the careful attention with which their material was handled and transcribed, as well as their accurate survey of previously published studies of cryptococcosis. It is the only complete exposé of the entire subject previously brought to my attention. Therefore, I recommend it to you—practitioner as well as the serious student of pathogenic mycology.

Alvis E. Greer, M.D.

PROCEEDINGS OF THE THIRD NATIONAL CANCER CONFERENCE, Detroit, Michigan, June 4-6, 1956. Sponsored by American Cancer Society and the National Cancer Institute, United States Public Health Service. Philadelphia and Montreal, J. B. Lippincott Company, 1957, 961 pages, $9.00.

Although the two preceding National Cancer Conferences were excellent, the Third National Cancer Conference far exceeded all the others, and anyone interested in cancer should become familiar with the Proceedings, which are voluminous. It is impossible, in a review, to do justice to the work, because it is so comprehensive. There are a group of general lectures which are excellent and which are presented by authorities in the various fields. These are epidemiology as a tool in cancer research, radiation neoplasia, the virus etiology of cancer, the chemical effects of growing tumors on the host with special reference to iron, factors influencing the curability of cancer, and the measurement of morbidity. Then there are a group of symposia and panels, one on cancer of the breast, in which the subject is discussed from all angles. Another panel is cancer of the prostate in which suprarenalectomy and hypophysectomy are discussed. There is also a symposium on lymphomas and leukemias. There is another symposium on chemotherapy and cancer and a symposium on cancer of the lung. There is another symposium on cancer of the head and neck, one on cancer of the female genital tract, one on the gastrointestinal tract, and finally one on the end results in the treatment of cancer. Thus, it is seen that one cannot miss studying this volume for a comprehensive review of the present concept of cancer.

Alton Ochsner, M.D.

CORONARY HEART DISEASE, by Milton Plotz, M.D. Published by Hoeber-Harper Books, New York, 1957, 350 pages, 107 illustrations, $12.00.

There has long been a need for a re-organization of the morass of information which has been accumulating on the subject of coronary heart disease. Dr. Milton Plotz has succeeded in producing an important work on the subject, which is comprehensive yet concise. The all-inclusive table of contents, exhaustive bibliography and intervening 353 pages attest to the unqualified success of this objective.

Thus, it contains a comprehensive coverage of basic anatomic and physiologic principles, etiologic factors, pathology, complications, new laboratory tests, prognosis, differential diagnosis, and specific medical and surgical therapeutic procedures. Twenty-five illustrative case reports with electrocardiograms stress many important points. For good measure, Dr. Plotz has included sections on medicolegal aspects as well as dynamic preventive care.

The format is most acceptable. Although many illustrations are borrowed, they are pertinent and informative. This well-written book is a must for anyone who evinces any interest in this important subject.

Nathaniel E. Reich, M.D.

EKG FIBEL, by Rolf Heinecker, M.D. and Ferdinand Hoff, M.D. Published by Georg Thieme, Stuttgart, 1956, 195 pages, 216 illustrations, $4.50.

The popularity of teaching clinical electrocardiography by the comic strip approach continues unabated, and the small beginners texts in German by Heinecker attests that this can be done well if combined with good reproductions of tracings and the meticulous use of various printer's techniques, which serve to emphasize another sketchy text. By contrast, the book illustrates again the generally poor techniques and inferior equipment to which we are exposed in this country, as well as the indifference displayed by many publishers toward ventures of this sort in the United States.

On the other hand, the reviewer sees little merit in treating the reader on a sub-elementary level and exposing him to a multitude of descriptive patterns, which includes those of some rather esoteric bipolar precordial leads, without providing him at the same time with some of the necessary background of the principles involved. Experimental and theoretical considerations of the electrophysiology of the heart have reached a stage where an almost complete omission of such aspects in a clinical text must be considered a needless deficiency.

Hans H. Hecht, M.D.

RADICULAR SYNDROMES WITH EMPHASIS ON CHEST PAIN SIMULATING CORONARY DISEASE, by David Davis, M.D. Year Book Publishers, Chicago, 1957, 269 pages, 69 figures, $6.50.

This short text emphasizes the radicular syndromes with particular reference to the cervical and thoracic regions. There are chapters devoted to the historical background of the concept of root pain, anatomy of the vertebral areas, possible causes of the pain, mechanics, symptomatology, diagnostic signs and roentgenologic aspects. Following are detailed sections on lower cervical and upper thoracic root syndromes with chest symptoms, cervical root syndromes and treatment.

Pain in the chest is a common complaint that often is the one symptom which prompts a patient to consult his physician. The author has emphasized the various symptomatic variants of the radicular syndrome as well as the various natural causes of the syndrome. This is done in text book fashion as well as with numerous case histories. It is interesting to note that some of these patients had recurrent hypertension and/or coronary arteriosclerosis. He is careful to attempt to separate those symptoms attributed to the radicular syndrome and the concurrent disease. There are long term follow-ups on many patients. This book is recommended.

Hugh A. Flack, M.D.

ANESTHESIA FOR SURGERY OF THE HEART, by Kenneth K. Keown, M.D. A monograph in American Lectures in Anesthesiology. Charles C Thomas, Springfield, Illinois, 1956, Foreword by Charles P. Bailey, 109 pages, $3.75.

The publication of this little book represents a milestone in the development of cardio-anesthesiology. No one could have been better qualified to write this book than Dr. Keown. His personal experience in this field, which started at the time the first successful modern mitral commissurotomy was done in 1948, includes the supervision at present of almost 1,000 patients undergoing heart operations per year. In this rapidly expanding specialty his short, succinct and sagacious monograph will serve as a source of much detailed counsel, not only for the safe handling of cardiac patients through their critical operative stress, but also for a cooperative understanding and a basis for concerted team action by both the surgeon and anesthesiologist.

The importance of such cooperation in the complex physiopathological changes is shown in the author's discussion of the tetralogy of Fallot: "Still another trying time is the period spent in closing the pericardial sac. Because more blood reaches the lungs, following the Brock operation, particularly if an immediate left to right shunt exists, the left ventricle dilates. Extreme cooperation between surgeons and anesthesiologist must be exercised or the heart action will fail because of the effect of the tamponade. The blood pressure, pulse rate and left ventricular output must be closely observed for signs of inadequacy. Direct vision of the heart by the surgeon is inadequate to ascertain the early effects of the pericardial closure. He must rely upon his colleague, the anesthesiologist, for his critical evaluation." Specific advice for the anesthesiologist, based on wide experience, is given throughout the pages. Thus: "If the preoperative palpatory systolic pressure, as ascertained with the patient unsedated, but in the same position as on the table, is less than 90 mm. Hg., no preoperative barbiturate is given."

In addition to a fine section on the cardiac irregularities and their diagnosis and management during anesthesia, there is in the chapter on each cardiac lesion, a lucid discussion of such data as the preoperative cardiac catheterization reports, particularly those points which are germaine to a good understanding of the physiologic burden the patient is to carry through the operation.

In summary, this relatively inexpensive monograph is highly recommended for the practitioner and surgeon as well as for the anesthesiologist who wishes to give his patient the best chance possible for a successful surgical result.

J. Maxwell Chamberlain, M.D.

KLINISCH-RÖNTGENOLOGISCHE DIFFERENTIALDIAGNOSTIK DER LUNGENKRANKHEITEN, by L. Dünner, M.D. Ferdinand Enke, Stuttgart, Germany, 1954.

This book is devoted to the clinical and roentgenological aspects of differential diagnosis of lung disease. The clinical portion of the text is quite meager. Noteworthy is the lack of inclusion of important laboratory procedures which are part and parcel of the clinical-roentgenological evaluation of problem cases.

The 269 pages devoted to chest x-ray films and text are taken up largely by 198 brief case reports. The organization of the contents follows the conventional pattern of morphological description of lobar pneumonia, abscess, cavities, bronchiectasis, atelectasis, miliary disease, carcinoma, round foci, hilar processes, pneumothorax, fibrosis and pleurisy. There is little if any attention paid to the pulmonary manifestations of metabolic, collagen and other systemic diseases which may be associated with pulmonary lesions.

Although the chest x-ray films are reproduced as negatives of the original, they are sufficiently clear and detailed not to offer difficulties in interpretation. However, many pages contain only one or two illustrations with the remainder of the page blank. The empty spaces could have been filled profitably with description of the conditions under consideration.

The author does not claim more for the book than it offers. In the present state of knowledge of differential diagnosis of pulmonary diseases, especially the many obscure conditions currently being encountered in routine chest x-ray surveys and even hospital admissions, a book of this type does not offer enough.

Eli H. Rubin, M.D.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Chest physician, F.C.C.P., Ohio-New York licenses, now assistant medical director, tuberculosis sanatorium, seeks responsible position (directorship, assistant directorship, head of department or clinic, etc.). Also will consider part-time position permitting part-time private practice. Please address inquiries to Box 292B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

British graduate, F.C.C.P., age 43, holding Canadian medical license, seeks permanent hospital or sanatorium appointment in Canada or United States. Extensive clinical and teaching experience in sanatoria and specialist chest hospitals. References. Please address inquiries to Box 293B, American College of Chest Physicans, 112 East Chestnut Street, Chicago 11, Illinois.

Tuberculosis specialist, age 44, F.C.C.P., now chief of 336-bed tuberculosis service, would like to work in a sanatorium in the general area of New York City or New Jersey for 6 months. Please address inquiries to Box 294B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Staff physician wanted for 215-bed hospital for chronic pulmonary diseases. Salary commensurate with qualifications and experience. Living quarters and laundry provided. Must be a graduate of approved school. Contact E. W. Hainlen, M.D., Director of Medical Services, Emily P. Bissell Sanatorium, 3000 Newport Gap Pike, Wilmington 8, Delaware.

Physicians wanted interested in pulmonary diseases for 170-bed state supported tuberculosis hospital, established 1½ years ago; active surgical program, outpatient service, x-ray and laboratory; consultants in all branches. US Citizenship and Alabama medical license or eligibility thereof required. Salary $8500 to $9500 depending upon qualifications, quarters to be made available. Apply: Medical Director, Sixth District Tuberculosis Hospital, 800 St. Anthony Street, Mobile, Alabama.

Physician wanted, full time, for moderate-sized chest disease hospital with research laboratory. Residency training in pulmonary diseases: tuberculosis, non-tuberculous pulmonary disease, and chronic heart disease. Preferably young man, 28-35, single. Must be graduate of approved school with at least one year internship. Living quarters and laundry provided. State salary on application. Write: Will Rogers Memorial Hospital, Saranac Lake, New York.

Anesthesiologist wanted. Our expanding surgical program requires the addition of a full-time anesthesiologist to our staff. Applicants must be graduates of approved schools and have or be eligible for Texas license. New, completely modern, air-conditioned hospital, located in rolling hills of scenic East Texas. Numerous lakes, streams and wooded areas provide excellent outdoor activities. Progressive city of over 55,000. Top-notch schools, churches, clubs. Apply at once to: Personnel Officer, East Texas Tuberculosis Hospital, Box 2003, Tyler, Texas.

1958 DIRECTORY LISTINGS

If you have not as yet returned your proof for your listing in the 1958 Directory of the College, please do so at once. Members may purchase copies of the 1958 College Directory by ordering immediately at the pre-publication price of $5.00. After publication the price will be $7.50.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Interim Session and Semi-Annual Meetings,
Board of Regents and Board of Governors
American College of Chest Physicians
Warwick Hotel, Philadelphia, December 2-3, 1957

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSES

12th Annual Postgraduate Course on Diseases of the Chest
Hotel Knickerbocker, Chicago, October 21-25

10th Annual Postgraduate Course on Diseases of the Chest
Park-Sheraton Hotel, New York City, November 11-15

3rd Annual Postgraduate Course on Diseases of the Chest
Ambassador Hotel, Los Angeles, December 9-13

CHAPTER MEETINGS

Kentucky Chapter, Louisville, September 18
Michigan Chapter, Grand Rapids, September 27
Colorado Chapter, Denver, September 28
Indiana Chapter, French Lick Springs, October 8
New Jersey Chapter, Trenton, October 15
Potomac Chapter, Baltimore, October 20
Virginia Chapter, Washington, D. C., October 27
Pacific Northwest Chapter, Portland, Oregon, November 8-9
Southern Chapter, Miami Beach, Florida, November 10-11

PLAN A TRIP TO TOKYO

For The

FIFTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Sponsored by the Council on International Affairs
American College of Chest Physicians

Presented under the Patronage of the
Government of Japan

TOKYO, JAPAN **SEPTEMBER 7-11, 1958**

President
Prof. Taizo Kumagai

Vice-Presidents
Prof. Hiroshige Shiota
Prof. Yoneji Miyagawa
Prof. Seizo Hatsunuma
Prof. Arao Imamura
Prof. Yas Kuno

Executive Officers
Prof. Masanaka Terada
Prof. Osamu Kitamoto
Prof. Masao Tsuzuki
Prof. Naotsugu Kawai

Financial Aid Committee
Taizo Ishizaka, Chairman

Secretary General
Jo Ono, M.D.

A Pre-Congress Tour of Japan

4 days—
KYOTO
NARA
NUMAZU
HAKONE
KAMAKURA

Diabutsu (Great Buddha), Kamakura

And The Post-Congress Tour

15 days

With planned scientific programs, social events and sightseeing . . .

arranged by College Chapters in . . . **HONG KONG**
BANGKOK
MANILA
HONOLULU

Upon completion of arrangements for the tours, a printed brochure containing all pertinent information will be made available this fall by Cartan Travel Bureau, Inc., Chicago, official travel agency for the Congress.

For further information please write to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois

THE EDITORIAL BOARD

FOR

DISEASES OF THE CHEST

is pleased to announce . . .

SECTION ON CARDIOVASCULAR DISEASES

to be published in each issue of the College Journal

DISEASES OF THE CHEST

effective

JANUARY, 1958

This new Section is being established because of the growth of the College and the varied interests of its members. The new Section will facilitate the selection of scientific papers of significance to our readers. The Editorial Board welcomes recommendations at all times relative to the improvement and maintenance of the high standards of the Journal.

J. Arthur Myers, M.D.
Editor-in-Chief

REDUCED RADIATION . . .

Radiation exposure reduced 70-80% with concentric mirror photofluorography

The Fairchild-Odelca photofluorographic camera, with its Bouwers Concentric Mirror Optical System, offers a practical solution to the problem of radiation in X-ray examination. Because its speed is four times that available in present refractive lens cameras, patient exposure to X-ray is reduced by 70-80%.

Diagnostic quality negatives

At the same time, resolution is more than doubled —which insures sharp, crisp negatives of diagnostic quality. The resolution of this system exceeds that of the fluorescent screen. The camera's speed also stops much voluntary and involuntary motion, virtually eliminating retakes.

Economically speaking, the Fairchild-Odelca is exceptional, for the 4" x 4" size means low film cost and minimum storage space. Pre-focusing and pre-positioning make operation simplicity itself . . . and there are no heavy cassettes to handle. (Also available in 70 mm. roll-film models for mass chest survey, hospital admissions and serial radiography.)

For details, contact your regular X-ray equipment dealer, or fill in the coupon below. Address Fairchild Camera and Instrument Corporation, Industrial Camera Division, 88-06 Van Wyck Expressway, Jamaica, New York, Dept. 160-50R1.

FAIRCHILD
X-RAY CAMERAS AND ACCESSORIES

Please send me:

_____ Bulletin on the Fairchild-Odelca 4 x 4 Camera.
_____ Bulletin on the Fairchild-Odelca 70 mm. Cameras.
_____ Technical data on mirror-optics photofluorography.

Name _____

Title _____

Street _____

City _____ Zone _____ State _____

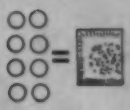
THE **SOLUTION** TO FRESH, WELL TOLERATED PAS CHEMOTHERAPY

PACKETTES OF Parasal® SODIUM CRYSTALS

(4.18 Gm. Sodium Para Aminosalicylate)
(Equal to 3 Gm. Active Free PAS)

ADVANTAGES OF PANRAY'S SPECIAL PACKETTES:

EXCELLENT TOLERATION — based on our high standards of purity, and color.



CONVENIENT—easy to open, no cutting necessary — each Packette replaces more than 8 tablets of Sodium PAS 0.5 Gm.

SUPERIOR SHELF LIFE—one year expiration date is now a fact. Ideal for the general hospital with occasional PAS usage.

HIGHLY RESISTANT to moisture vapor — 20% more protection than polyethylene of the same thickness.

SEALED-IN FRESHNESS and purity with each dose — no contamination or deterioration after box is opened.

INDIVIDUAL DOSE for rapid dissolution in cold water, juices or effervescent drinks — mix to taste.

ECONOMICAL — no deterioration upon exposure to moist, warm air — no waste — no weighing and mixing — no stained clothes.

CLEAR TRANSPARENCY — each white crystal can be seen—unlike polyethylene, no hidden discoloration possible.

TARGET POINT CHEMOTHERAPY

Write for samples, literature, complete information

The Panray CORP. 340 Canal Street New York 13, N.Y.

Sole Canadian Distributor Winley-Morris Co. 292 Craig St. West Montreal 29, P. Q.